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VOLUME 40
1940

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL

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SUCCESSFUL AUTOTRANSPLANTATION OF THE ADRENAL GLAND IN THE DOG

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Autotransplantation of the adrenal gland in the rat and in the guinea pig has been reported by a number of investigators¹. However, it is generally accepted that such a graft undergoes partial necrosis which is followed by regeneration of cortical tissue only. A successful transplantation of the whole adrenal gland in small animals has not been described.

Crowe and Wislocki² were among the first to attempt to transplant the adrenal in the dog. They observed that when fragments of the gland were placed in muscle only the cortical tissue survived. Such transplants were found to be functionless. Oldberg³ and Blodinger and his co-workers⁴ also were unable to obtain functioning autogenous grafts of the adrenal in the dog. Recently, however, Levy and Blalock⁵

From the Laboratory of Surgical Research and the Department of Surgery of the Harvard Medical School.

1 Jaffe, H. L. Transplantation of the Guinea Pig Suprarenal and Functioning of Grafts, *J. Exper. Med.* **45**: 587, 1927. Wyman, L. C., and tum Suden, C. Studies on Suprarenal Insufficiency. Growth of Transplanted Cortical Tissue in Rat, *Am. J. Physiol.* **101**: 662, 1932. Ingle, D. J., and Higgins, G. M. Autotransplantation and Regeneration of Adrenal Gland, *Endocrinology* **22**: 458, 1938.

2 Crowe, S. J., and Wislocki, G. B. Experimental Observations on Suprarenal Glands with Special Reference to the Functions of Their Interrenal Portions, *Bull. Johns Hopkins Hosp.* **25**: 287, 1914.

3 Oldberg, E. An Attempt to Transplant the Adrenal, *Am. J. Physiol.* **91**: 225, 1929.

4 Blodinger, I., Klebanoff, H. E., and Laurens, H. Suprarenal Transplantation in the Dog, *Am. J. Physiol.* **76**: 151, 1926.

5 Levy, S. E., and Blalock, A. A Method of Transplanting the Adrenal Gland of the Dog with Reestablishment of Its Blood Supply, *Ann. Surg.* **109**: 84, 1939.

have reported transplantation of the kidney together with the adrenal to the neck (with reestablishment of the blood supply by suture of vessels) and subsequent removal of the kidney. In their preparations both the cortex and the medulla of the adrenal remained viable. The method of transplanting the adrenal gland described here resembles that of Levy and Blalock⁵ in that viable grafts of both the cortex and the medulla were obtained. This was accomplished, however, by grafting the adrenal to the ovary without suture of blood vessels.

MATERIAL AND METHOD

The general procedure was as follows. Mongrel bitches weighing between 5 and 10 Kg. were used in all experiments. The operations were performed aseptically with the animals under intravenous sodium pentobarbital anesthesia. The adrenal was approached through a transperitoneal upper right rectus or oblique subcostal incision. By careful dissection the lower pole of the adrenal gland was partially mobilized. The neurovascular connections to the remainder of the gland were not disturbed. In none of the preparations was the lumbo-adrenal vein ligated or separated from the adrenal gland at this stage. The ovary on the experimental side was then mobilized and drawn up to the adrenal, care being taken not to interfere with its vascular supply. The ovarian bursa was incised, the ovary being exposed. A small portion of both ovary and adrenal was then excised so as to create raw bleeding surfaces, which were united by mattress sutures of fine silk. At a second operation, two to four weeks later, the adrenal was separated from its remaining normal neurovascular connections and, together with the adherent ovary, was brought into the peritoneal cavity. Its position there was maintained by suturing it to the anterior abdominal wall. Excision of the opposite adrenal gland was performed either before or after the final transplantation, usually as a separate procedure. Variations of this procedure and the results obtained are shown in the accompanying table. It will be noted that whenever the vascular supply of the adrenal was divided at the first operation the experiment failed. It is necessary first to furnish the adrenal with a new blood supply through the ovary and then to separate it from its normal neurovascular supply.

RESULTS

Twelve experiments were performed, 4 of which were successful. Several factors account for the 8 failures. Experience with the operative technic is essential. Operation in stages not only permits the establishment of a new blood supply from the ovary to the adrenal but minimizes operative shock. As already noted, all attempts to accomplish grafting and division of the blood supply of the adrenal in one stage failed (experiments 1, 2, 3 and 10). The method of joining the adrenal to the ovary is of considerable importance. In the early experiments this was accomplished by excising a small fragment of both adrenal and ovary and then uniting the raw surfaces with mattress sutures. In only 2 of 5 attempts (experiments 4, 5, 6, 7 and 8) was the new vascular supply sufficient to maintain the life of the graft. In 3 instances the glands were partially bisected and the cut edges interlocked, or "sandwiched," together. This "sandwich" method proved more efficacious.

Autotransplantation of the Adrenal Gland in the Dog

Procedure	Experiment No	Survival Period	Result	Comment
Two stage operations	1	7 days	Failure	All attempts to divide blood supply to adrenal at same time that it was attached to the ovary failed
1 Right adrenalectomy				
2 Mobilization and grafting of left adrenal (neurovascular supply of adrenal divided)	2	1 day	Failure	
	3	9 days	Failure	
Three stage operations	4	9 days	Failure	
1 Mobilization of right adrenal and grafting to ovary (adrenal blood supply left intact)		Living 15 months after last operation	Success	
2 Left adrenalectomy				
3 Grafted adrenal separated from its normal vascular supply and brought into the peritoneal cavity				
Three stage operations	6	Died after 2d stage operation	Failure	
1 Bilateral mobilization and grafting of adrenals to ovary (adrenal vascular supply left intact)	7	9 days	Failure	
2 Excision of one graft and ovary	8	10 months, killed (died 3 days after excision of transplant)	Success	Physiologic activity of graft proved by death of the animal from adrenal insufficiency
3 Separation of remaining graft from its normal vascular supply and transplantation into the peritoneal cavity				
Three stage operations	9	2 days	Failure	
1 Right adrenalectomy left adrenal mobilized and attached to ovary (adrenal blood supply intact)				
2 Partial freeing of graft				
3 Complete freeing of graft from its normal vascular supply				
One stage operations ('sandwich technic') Right adrenalectomy Mobilization and grafting of left adrenal	10	6 days	Failure	Failure attributed to fact that vascular supply of gland was divided at time of grafting
Four stage operations ('sandwich technic')	11	Living 14 months after last operation	Success	Physiologic activity of graft proved as in experiment 8 see text for details
1 Left adrenal grafted to ovary (blood supply intact ['sandwich technic'] see text)	12	1 year killed (died 10 days after excision of transplant)	Success	
2 Right adrenal grafted to ovary (blood supply intact ['sandwich technic'] see text)				
3 Right transplant separated from blood supply and together with ovary brought into peritoneal cavity				
4 Excision of left adrenal and ovary				

Two of 3 attempts (experiments 10, 11 and 12) were successful, and the single failure can be ascribed to the fact that the entire procedure was performed in one stage

It is interesting that in 2 of the 4 successful experiments (experiments 11 and 12) the opposite adrenal was not excised until after transplantation of the graft into the peritoneal cavity, so that at the time of transplantation there was no acute physiologic need for the graft. Similar exceptions to Halsted's⁶ "law of deficiency" have been noted by Shambaugh⁷ in working with the parathyroid and by Levy and Blalock⁵ in experiments performed with the adrenal

The 4 animals on which successful transplantations were performed have remained in good health for ten, twelve, fourteen and fifteen months respectively since the removal of the opposite adrenal gland. All have either maintained their original weight or gained weight. In 2 instances conclusive evidence of the activity of the cortical portion of the transplant was obtained when death from cortical insufficiency occurred in five and ten days respectively after excision of the grafted tissue (experiments 8 and 12). During this period the dogs showed anorexia and weakness, and there was a terminal fall in the level of blood chlorides and in the blood pressure. The observations at autopsy were those usually associated with adrenal insufficiency. There were ulcerations of the mucosa in the upper part of the gastrointestinal tract, marked congestion of the pancreas and moderate congestion of the kidneys and liver. The spleen was small and contracted. In 1 dog the thyroid was four to five times the normal size. The enlargement was symmetric, involved both lobes and grossly and microscopically had the appearance of a colloid goiter. There was no hyperplasia, cyst formation, hemorrhage or adenoma. No accessory or remaining adrenal tissue was found. Gross and microscopic examination of the pituitary showed no variation from the normal.

At the time of removal (experiments 8 and 12) the transplanted adrenal tissue was easily recognized. On cut section the medulla was somewhat reduced in size, but the sharp contrast between it and the cortex was well preserved. On microscopic examination (eosin-methylene blue and hematoxylin and eosin stains) the cells of both the cortex and the medulla appeared normal. There was no hypertrophy or hyperplasia. Ganglion cells and unmyelinated nerve fibers were seen in the capsule and medulla of the transplants. Myelinated nerves could not be demonstrated with certainty. This is in accord with the studies of

6 Halsted, W. S. Auto- and Isotransplantation, in Dogs, of the Parathyroid Glandules, *J. Exper. Med.* **11** 175, 1909.

7 Shambaugh, P. Autotransplantation of Parathyroid Gland in the Dog. Evaluation of Halsted's Law of Deficiency, *Arch. Surg.* **32** 709 (April) 1936.

Elliott,⁸ who showed that after denervation of the adrenal there is a degeneration of myelinated nerve fibers up to their termination in the medulla. Similar observations were made by Hollinshead,⁹ who noted that unmyelinated fibers persist after removal of the upper lumbar sympathetic chain and both splanchnic nerves and denudation of the adrenal. Such nerves probably arise from intrinsic ganglion cells. Levy and Blalock⁵ found only unmyelinated nerves in transplanted adrenals. A layer of very vascular connective tissue joined the adrenal to the ovary. In the latter there were numerous young follicles, some of which appeared cystic.

The behavior of the animals in which transplantation has been successfully carried out has not been altered. Levy and Blalock⁵ observed a normal pregnancy in a dog with a transplanted adrenal, but none of our animals have been in heat, perhaps because of the utilization of the ovaries in the autotransplantation. At the time of writing the blood pressure of these dogs is maintained at normal levels, and no significant variations of the "fasting levels" of sugar, nonprotein nitrogen, albumin, globulin, calcium and phosphorus in the blood have been noted. As the histologic observations indicate a successful transplantation of the entire gland, these animals should react physiologically in the same manner as do animals in which complete denervation of one adrenal and excision of the other have been performed. Further studies of the metabolism of these dogs, particularly in relation to the functional activity of the transplanted medulla, are in progress.

SUMMARY

A method is described of autotransplantation of the adrenal gland of the dog by grafting it to the ovary without suture of blood vessels. Twelve experiments were performed, 4 of which were successful in that the graft maintained the life of the animal after removal of the opposite adrenal. In 2 dogs the transplant was excised and was found to be composed of viable cells of both the cortex and the medulla. The activity of the cortical portion of the graft was proved. Further studies of the metabolism of these dogs, particularly in relation to the functional activity of the medullary portion of the graft, are in progress.

8 Elliott, T. R. The Innervation of the Adrenal Glands, *J. Physiol.* **46** 285, 1913.

9 Hollinshead, W. H. The Innervation of the Adrenal Glands, *J. Comp. Neurol.* **64** 449, 1936.

MASTECTOMY

A CLINICAL PATHOLOGIC STUDY DEMONSTRATING WHY MOST
MASTECTOMIES RESULT IN INCOMPLETE REMOVAL
OF THE MAMMARY GLAND

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Simple mastectomy is an operation frequently attempted but seldom accomplished. Bold as this declaration may seem, it is true.

Theoretically the term "mastectomy" indicates complete excision of the mammary gland and does not apply to incomplete removal, partial resection or subtotal ablation. In practice however, the vast majority of so-called "mastectomies" accomplish nothing more than incomplete extirpation of the main mass of mammary tissue. While the surgeon aims to remove all of the mammary gland, he invariably leaves some of it behind to undergo either normal involution or pathologic change.

During the past three years, careful anatomic and histologic studies have been made of all breasts sent to the pathologic laboratories of several large hospitals. The mastectomies had been done by well trained surgeons, many of whom had had considerable experience in surgical treatment of the breast. In practically every instance no difficulty was encountered in demonstrating that the breast had been incompletely removed and remnants of mammary tissue left in the operative area. This is no criticism of the excellent technic and ability of the operating surgeons, rather, it emphasizes certain anatomic peculiarities of the breast. I myself was by far the most persistent offender.

Embryologically the breast represents a modified sebaceous gland which has assumed a highly specialized function. Its ultimate size, shape and ramifications depend largely on the age and physical status of the patient and the functional experiences of the gland. It is composed of fifteen to twenty lobules, each of which has a separate ductal opening on the surface of the nipple. As a general rule, six to eight of these lobules assume fully 95 per cent of the functional load, the remaining segments being small and poorly developed.

Accurate anatomic patterns of the lactiferous ducts can readily be obtained by means of roentgen studies with a contrast medium¹. The mammograms give a clear visualization of the ducts, denoting their size,

¹ Skiodan viscous for this purpose was supplied by the Winthrop Chemical Co., New York.

number, conformation and distribution (fig 1) During the past three years more than 385 mammograms have been made, and the ramifications of the lactiferous ducts have been carefully studied² It is evident that the mammary gland does not occupy a small localized area on the anterior wall of the chest. Instead, its ducts are widely distributed over the entire anterolateral aspect of the thoracic cage. In fully 95 per cent of cases the visualized ducts ascended into the axilla, and in some



Fig 1—Mammogram showing the injected lactiferous ducts passing around the pectoral muscles as they extend into the axilla. A fibroadenoma occupies the lower mammary segment.

instances they followed the brachial plexus and blood vessels into the apex of the axillary fossa. All obstetricians appreciate the frequency with which this axillary segment becomes swollen and engorged during the early phase of active lactation. In 15 per cent of cases the ducts were seen to pass downward and medially into the epigastric space, and

² Hicken, N. F. Mammography. *The Roentgenographic Diagnosis of Breast Tumors by Means of Contrast Substances*, Surg., Gynec. & Obst. **64**: 593-603, 1937.

in 2 per cent they followed the lateral wall of the chest beyond the anterior borders of the latissimus dorsi muscle. In 2 instances the ducts were seen to cross the midsternal line, but in no instance were there anastomotic communications with the opposite breast.³ It was surprising to see the frequency with which the injected ducts came in intimate contact with the overlying skin. This was particularly true of the lactating gland (fig 2).

These mammographic studies clearly demonstrated that the lactiferous ducts spread over the entire anterolateral wall of the chest. It follows therefore that simple mastectomy requires denudation of an extremely



Fig 2—Breast after injection of the ducts with a contrast medium. Note how closely the large duct and its ramifications approach the skin. This represents the ramifications of only one lobule of the breast of a multipara during its quiescent state.

large part of the thoracic wall if all mammary structures are to be completely removed.

An appreciation of the anatomic distribution of the lactiferous ducts combined with observation of the conservative type of operation employed in the usual mastectomy suggested to me that in many instances only a portion of the mammary gland had been excised.

³ Hicken, N. F. Mammography. The Preoperative Visualization and Diagnosis of Breast Tumors by Means of Contrast Roentgenograms. *Nebraska M. J.* 22: 211-214, 1937.

Incontrovertible evidence as to the incomplete removal of the breast was easily obtained by study of the excised specimens which were routinely sent to the pathologic laboratories. This was done by cannulizing each of the ducts as it opened on the surface of the nipple and injecting it with a solution of methylene blue. If the mammary gland had been removed in its entirety, the ductal system remained intact, hence none of the dye could escape. If, however, the lactiferous ducts had been severed or if a portion of a lobule had been left in situ, the colored solution escaped, thus accurately indicating the area of incomplete removal.

Seventeen breasts which were supposed to have been completely excised by "mastectomy procedures" were examined in this manner. There was not a single instance in which the mammary tissue had been removed in its entirety. In 94 per cent of cases the dye escaped in the subareolar zone, indicating that some of the breast had been left attached to the reflected skin flaps. The axillary segment had been incompletely removed in 88 per cent of cases, the sternal extension in 23 per cent and the epigastric ramifications in 11 per cent. It was found that in 75 per cent of the specimens there were multiple areas of incomplete removal, and in 3 instances the dye escaped from the entire periphery of the breast, indicating a most inadequate operation.

According to these studies, there were certain segments of the breast which the surgeon was prone to remove incompletely, namely, the axillary extension, the subcutaneous zone, the sternal segment and the epigastric ramifications.⁴ These are demonstrated in figure 3.

It would seem that if the breast is sufficiently diseased to necessitate amputation every precaution should be exercised to see that all mammary tissue is removed. Occasionally, residual mammary tissue undergoes pathologic transformation, necessitating subsequent operations and even eventuating in adenocarcinoma. The following cases are representative.

REPORT OF CASES

CASE 1—Mrs F J, a housewife 46 years of age, the mother of three children, entered the hospital because of a "rapidly growing lump in her right axilla." Fifteen years previously the right breast had been amputated because of painful "chronic cystic mastitis." Examination demonstrated a hard tumor mass measuring 1 inch (2.5 cm) in diameter, situated in the anterior axillary fold (fig 4). It was firmly adherent to the underlying pectoral muscles but was not attached to the skin. Beneath the pectoral muscles there were two indurated, nontender lymph glands. A radical exenteration of the axilla with removal of the pectoral muscles was performed. The tumor mass was found to consist of normal mammary tissue impregnated with adenocarcinoma which had spread to the regional lymph glands.

4 Hicken, N F, Best, R R, Hunt, H B, and Harris, T T. The Roentgenological Visualization and Diagnosis of Breast Lesions by Means of Contrast Media, *Am J Roentgenol* 39 321-343, 1938.

CASE 2—Miss A. M., 54 years of age, sought advice because of a "painful lump under her arm." Ten years previously the left breast had been removed because of "infected chronic cystic mastitis." Since that time she had always had

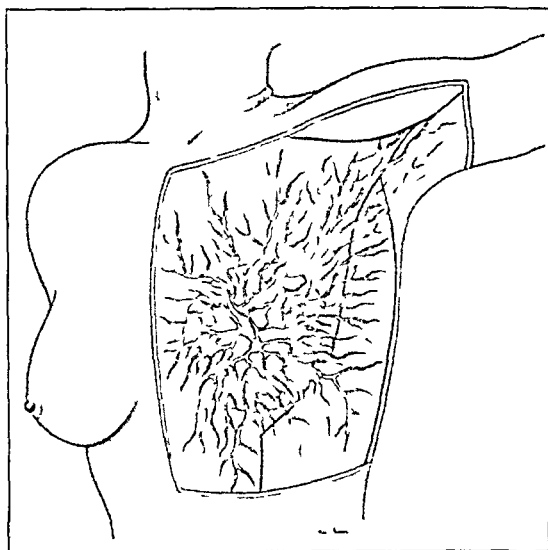


Fig 3—Composite schematic drawing representing the ramifications of the lactiferous ducts over the anterolateral chest wall. Note the axillary, subpectoral, midsternal and epigastric extensions. These were all seen by mammographic studies.

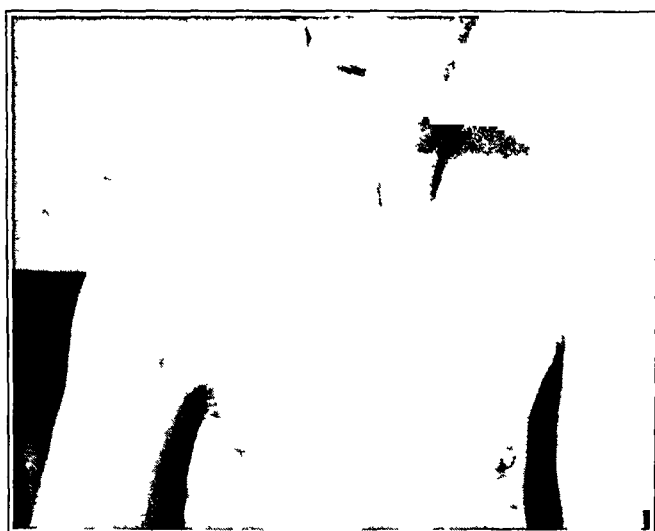


Fig 4—Patient in whom, fifteen years previously, incomplete removal of the right breast had been done for "chronic cystic mastitis." Adenocarcinoma developed in the residual mammary tissue.

a sense of discomfort in the left axillary region. During the past three months the tumor mass had rapidly increased in size and had become tender and painful. Exploration demonstrated the neoplasm to be composed of mammary tissue which

contained several small distended cysts. From the thick, tenacious cystic fluid pure cultures of streptococci were obtained.

It is obvious that in each of these cases the axillary segment of the breast was overlooked during the primary mastectomy, and the residual tissue underwent pathologic change. Complete mastectomies would certainly have prevented these catastrophes.

TECHNIC

As a result of these studies, it was learned that a complete mastectomy can be performed if certain points are observed. The following plan has been effective.

The entire mammary gland and axilla are prepared as for a radical amputation of the breast. The nipple is thoroughly cleansed of all incrustations, and inspissated plugs of debris are gently expressed from the orifices of the lactiferous ducts. Two of the patent estuaries in each quadrant of the nipple are cannulized and injected with a solution of methylene blue. The dye accurately outlines the ramifications of the mammary tissue. If the ducts are inadvertently incised during the operation, the escaping dye affords an excellent visual warning that incision is still within the confines of the mammary gland. If the surgeon keeps beyond the "blue zone" a complete mastectomy is assured.

The practice of amputating the breast through a small incision accounts for the incompleteness of most mastectomies. Such conservatism is prompted by a desire to give the patient a small, invisible scar. The transverse cutaneous incision usually fails to give adequate exposure of the axilla, and if the incision is carried far enough medially to expose the sternum and epigastric notch the scar is plainly visible when low-necked dresses are worn. These disadvantages have been overcome by the use of an oblique incision (fig 5). The outer margin of the incision begins 1 inch (2.5 cm.) below the floor of the axilla and extends downward and medially toward the epigastric notch.

Extreme care is essential in reflecting the skin flaps, for adequate exposure is desirable. Usually the course of the cutaneous vessels has been previously outlined by transillumination studies, so that they will not be injured and viability of the flaps will be assured. The dissection is carried along in the subcutaneous zone close to the skin, so as not to leave any mammary tissue. The larger lactiferous ducts and their fine ramifications are clearly visualized by their methylene blue content, hence their integrity is preserved. It is surprising to learn that the skin flaps must be practically devoid of subcutaneous tissue if one desires to avoid the matrix of the breast.

It is imperative that the skin flaps be reflected so as to expose the axilla, the sternum, the epigastric notch and the anterior border of the

latissimus dorsi muscle The wide denudation affords complete access to all segments of the breast, and one is surprised to find its ramifications so extensive

Beginning beyond the "blue zone," at the midsternal line, the breast is carefully reflected (fig 5 *B*) from the fascial covering of the pectoral muscles (On two occasions the "blue colored milk ducts" have been seen to penetrate this pectoral fascia and enter the muscular substance⁵

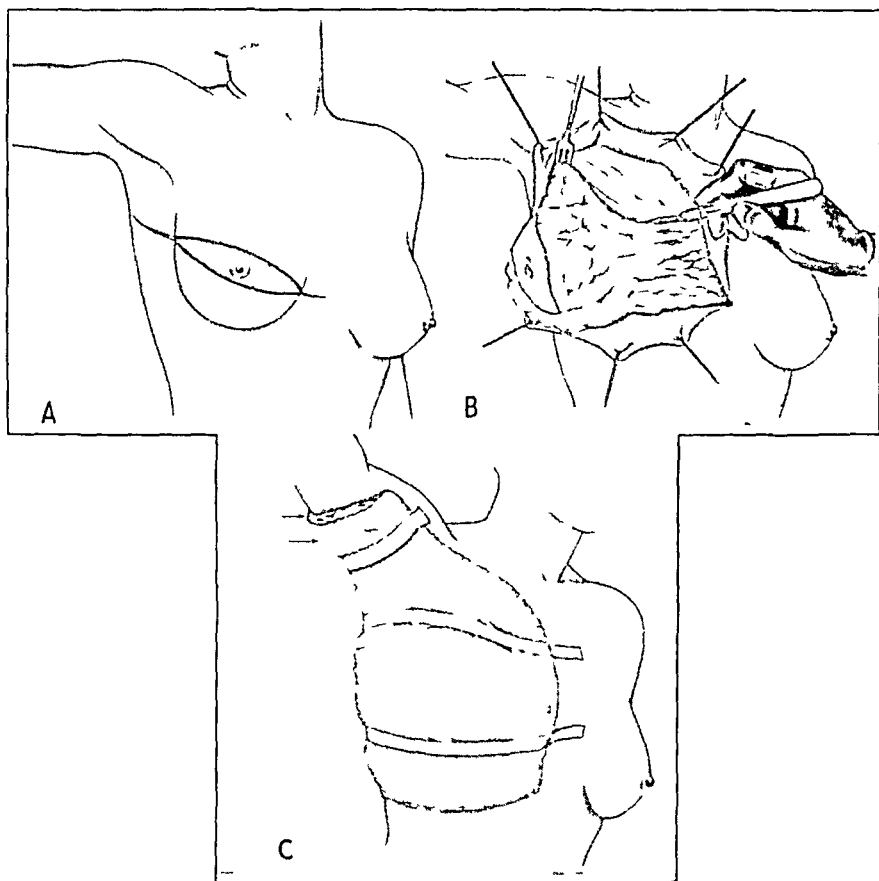


Fig 5—*A*, oblique mastectomy incision which gives adequate exposure without leaving scars that will show *B*, manner of dissecting the breast from the pectoral fascia Note the axillary and epigastric extensions of mammary and adipose tissue *C*, compressive rubber sponge dressings employed to keep the skin flaps in intimate contact with their nutritional bed

In these cases the fascia and penetrating lacteals were excised) Care should be exercised to remove all mammary tissues from the epigastric space and along the lateral wall of the chest As the mobilized breast is

⁵ Wainwright, J M Carcinoma of the Male Breast, *Ann Surg* **14** 837-859, 1927

pulled upward and outward its axillary segment can be easily followed and removed. Occasionally some of the matrix will extend between the two pectoral muscles, in which event it should be extirpated. Invariably the axillary segment extends well into the axilla. In some instances it has been necessary to dissect the dye-stained lactiferous ducts from the axillary vein, but as a rule they do not extend so far. If the axilla is not entered, one is almost certain to overlook mammary tissue. Complete removal of the mammary gland leaves a large area of traumatized tissue which of necessity will produce serum. If the serious effusions are permitted to accumulate, they separate the skin flaps from their nutritional bed and favor sloughing. Dependent counterdrainage overcomes such danger. I have found that compressive rubber sponge dressings not only minimize postoperative hemorrhages and serious effusions but hold the skin flaps in firm apposition to the wall of the chest, thus favoring rapid restoration of their nutrition. These large sponges cover the entire operative area and are held securely in place by adhesive strapping (fig 5 C). If they are applied too tightly the pressure obliterates the cutaneous vessels and favors necrosis of the skin, if too loosely, they permit serum to collect. Experience soon teaches the proper application.

During the first twenty-four hours the arm should be abducted to an angle of about 90 degrees. This tends to stretch the pectoralis major muscle so that when the skin becomes adherent to it free and painless motion will result. Several times during the day the arm may be placed against the wall of the chest and gentle passive exercises given. This minimizes muscular fatigue and assures early restoration of function.

SUMMARY

Contrast mammographic studies of 385 breasts indicate that the lactiferous ducts spread over the entire anterolateral wall of the chest. In 95 per cent of the mammograms the ducts passed up into the axillary fossa, in 15 per cent they were seen to extend downward into the epigastric space, in 2 per cent they coursed along the lateral wall of the chest beyond the limits of the anterior border of the latissimus dorsi muscle, and in 2 instances they passed across the midsternal line to the opposite side. In no instance was there an anastomotic communication between the two breasts.

A simple mastectomy should aim to remove the entire mammary gland. Unfortunately, this is seldom accomplished. The lactiferous ducts of 17 breasts which had been removed by "routine mastectomy" were injected with a solution of methylene blue. Wherever the breast tissue had been incompletely removed, the dye escaped from the severed ducts. It was found that in 94 per cent of cases mammary tissue had been left attached to the reflected skin flaps. In 88 per cent the axillary

appendage of the breast had been incompletely excised, in 23 per cent the sternal extensions had been severed, and in 11 per cent the epigastric ramifications had been left behind. In 75 per cent of all the cases studied there were multiple areas of incomplete removal.

A technic is described which assures complete removal of the mammary gland. This includes preoperative injections of methylene blue into the lactiferous ducts and operation with the incision kept well beyond the "blue zone."

Compressive sponge dressings minimize the hazards of postoperative hemorrhage and serous effusion and hold the skin flaps in intimate contact with their nutritional bed.

Residual mammary tissue may undergo either normal involution or neoplastic change. Cases are reported in which adenocarcinoma and chronic cystic mastitis developed in residual mammary tissue in patients who years previously had been subjected to "mastectomy."

508 Medical Arts Building

INFECTION AS A CAUSE OF MASSIVE HEMORRHAGE IN CHRONIC PEPTIC ULCER

REPORT OF FIVE CASES

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AND

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This communication is a report of 5 cases of death from hemorrhage due to infection in chronic gastric and duodenal ulcers. They were among the last 7 cases of exsanguinating hemorrhage from ulcers observed in the past seven and one-half years at the New York City Hospital, Welfare Island. In each of the 5 cases the criteria of chronicity were answered—distortion of the architectural pattern of the wall, fibrosis of the base of the ulcer and some degree of chronic inflammatory cellular reaction. In all cases bacteria were demonstrated in the sections at the point of hemorrhage. Clinical evidence in some of the cases proved the presence of septicemia.

REPORT OF CASES

CASE 1—A white man 71 years old was admitted to the surgical division of the City Hospital, service of Dr. A. S. Morrow, on May 29, 1932, in profound shock. He gave a history of vomiting a large amount of blood the previous evening and of a tarry stool. The only other significant symptom was epigastric pain, which had been present for the past four years. There had never been a previous hemorrhage.

He appeared almost exsanguinated. He complained of thirst. The blood pressure was low and the temperature subnormal. Tachycardia was observed. The value for hemoglobin was 35 per cent. With sedatives and a transfusion he improved slightly, then hemorrhage recurred, and death ensued twelve hours after admission.

Necropsy—On the posterior wall of the first portion of the duodenum was a chronic ulcer measuring 5 cm. in diameter. In the center was an eroded vessel. The small and large intestines were filled with partially clotted blood.

Histologic Examination—The ulcer was chronic, the base was replaced by dense scar tissue covered by a thin necrotic membrane. The artery was thick and sclerotic, its wall was involved by necrosis. The lumen of the artery throughout its extent contained gram-negative bacilli and gram-positive cocci (fig. 1).

From the Pathologic Laboratory and the First Medical Division of the City Hospital.

Pathologic Diagnoses—The pathologic diagnoses were chronic duodenal ulcer with erosion of the artery from infection and exsanguinating hemorrhage

CASE 2—A white man 47 years of age was admitted to the second medical division of the City Hospital, service of Dr John McCabe, on Dec 31, 1934. For four days he had complained of nausea, vomiting and pains in the chest, abdomen and back. These symptoms had occurred during a drinking bout. The

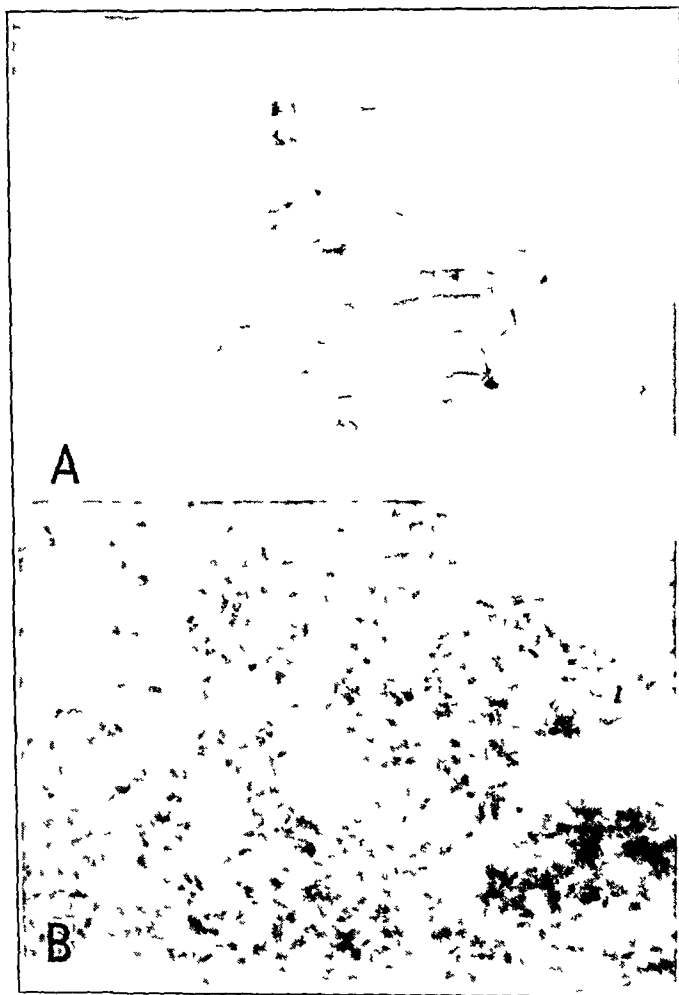


Fig 1 (case 1)—A, low power photomicrograph of the ulcer, showing the course of the artery and the point of rupture. B, bacilli and cocci found throughout the course of the artery (Gram's stain)

had been accompanied with nausea and vomiting and followed by chills, fever and pain. The patient was chronically alcoholic. The other data were irrelevant.

He was acutely ill. The temperature was 102 F, the pulse rate 130 and the respiratory rate 28. There were signs of pneumonic consolidation of the left lung. The sputum was bloody. The liver was large and tender. Culture of the blood revealed Friedlander's bacillus.

The course remained typically pneumonic until the fifth day, when the patient suddenly raised about 12 ounces (360 cc) of fresh blood. He became very apprehensive, and the pulse became almost imperceptible. Death followed in two and one-half hours.

Necropsy—The stomach contained about 1 liter of partially clotted blood. There were seven chronic ulcers. The largest was on the posterior wall, just below the esophageal orifice. It measured 3 by 5 cm and had a large eroded artery in the base. Two smaller ulcers involved the posterior wall, close to the lesser

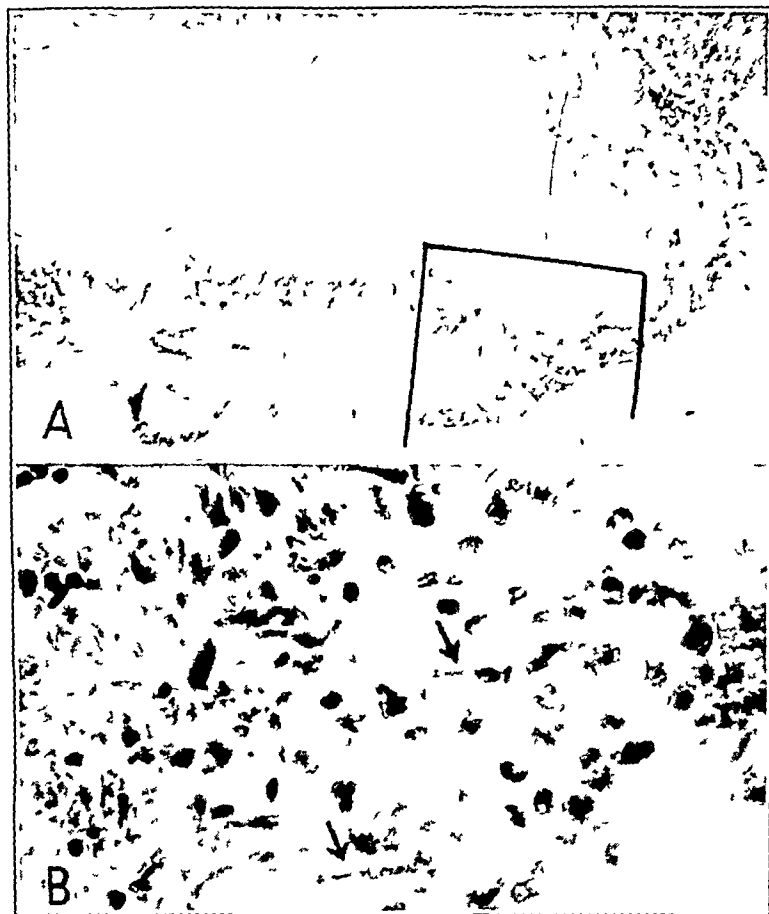


Fig 2 (case 2) —*A*, acute infectious aneurysm of the artery in the base of the ulcer. *B*, bacilli in the region marked in the first photomicrograph (Gram's stain)

curvature. Four smaller ulcers were prepyloric. The small intestines and the cecum were filled with fresh blood. The contents of the large intestine were

Histologic Examination—The histologic appearance of the largest ulcer only is described. The large artery showed an acute necrotic lesion containing many leukocytes and destroying the entire thickness of the wall. Within this zone were numerous gram-negative encapsulated bacilli morphologically identical to Friedlander's bacillus (fig 2).

Pathologic Diagnoses—The pathologic diagnoses were pneumonia due to Friedlander's bacillus, with septicemia and acute pericarditis, multiple chronic gastric ulcers, acute infectious aneurysm of a branch of the gastric artery in the chronic ulcer, with rupture and exsanguinating hemorrhage, chronic gastritis, syphilis of the aorta, and chronic prostatitis

CASE 3—A white man 53 years old was admitted to the second medical division of the City Hospital, service of Dr B F Donaldson, on Feb 17, 1938, because of weakness, anorexia, loss of weight and diarrhea, all of three weeks' duration. In the past half year he had lost 25 pounds (11.3 Kg) in weight.

He was emaciated and very anemic. Physical examination showed little abnormality. The apex of the left lung revealed wheezing expiration. The blood pressure was 72 systolic and 50 diastolic. The abdomen was somewhat spastic, and palpation was unsatisfactory. The temperature was 100.6 F, the pulse rate 80 and the respiratory rate 24. The value for hemoglobin was 40 per cent. There were 2,500,000 erythrocytes per cubic millimeter of blood. The urine was normal. Electrocardiographic tracings were normal. Chemical study of the blood revealed no abnormality. The Wassermann reaction was negative. A roentgenogram of the chest was normal. The stool consistently gave a positive reaction for blood.

For one month the patient had a fever of unknown origin, with daily fluctuations of temperature between 99 and 102 F. The anemia and weakness increased in spite of all measures. One month after admission he had a severe chill and the temperature rose to 105 F. Culture of the blood revealed hemolytic streptococci. Under administration of prontosil (the disodium salt of 4-sulfamidophenyl-2'-azo-7'-acetyl-amino-1'-hydroxynaphthalene-3',6'-disulfonic acid) the temperature gradually fell, but the general condition appeared worse. Repeated cultures of the blood showed decreasing numbers of organisms but never became sterile. Pallor and weakness continued to increase, and death occurred on April 15.

Necropsy—The stomach contained massive blood clots. On the lesser curvature, 8 cm from the pylorus, was a chronic ulcer 3 cm in diameter with a nest of petechial hemorrhages near the proximal edge. The right psoas muscle was replaced by a tuberculous abscess cavity containing greenish pus from which a hemolytic streptococcus was isolated on culture.

Histologic Examination—Buried in the granulation tissue of the ulcer in the region of the petechial hemorrhages were masses of gram-positive streptococci, filling many of the capillaries. The surface of this region was covered by fibrin containing a few organisms (fig 3).

Pathologic Diagnoses—The pathologic diagnoses were chronic gastric ulcer with acute streptococcic infection and massive hemorrhage and chronic tuberculous abscess of the psoas muscle with hemolytic streptococcus infection.

CASE 4—A white man 76 years of age was admitted to the second medical division of the City Hospital, service of Dr J H Cudmore, on March 26, 1939, because of black vomitus, loss of weight, tarry stools and edema of the ankles, present for five years. He was pale and undernourished. On examination there were pitting edema of the ankles, tachycardia, a normal temperature and normal respirations. Examination otherwise gave essentially negative results. Early the next morning he vomited a large amount of fluid and clotted blood. Two and one-half hours later there was a second attack, and he died within thirty minutes.

Necropsy—The stomach was filled with fluid and clotted blood. A large chronic ulcer encircled the pylorus. The border was firm and raised. The base was formed by the head of the pancreas. In the upper portion of the ulcer was an eroded vessel.

Histologic Examination—Section through the region of the eroded ulcer showed simple chronic ulcer with complete destruction of the muscular wall and replace-

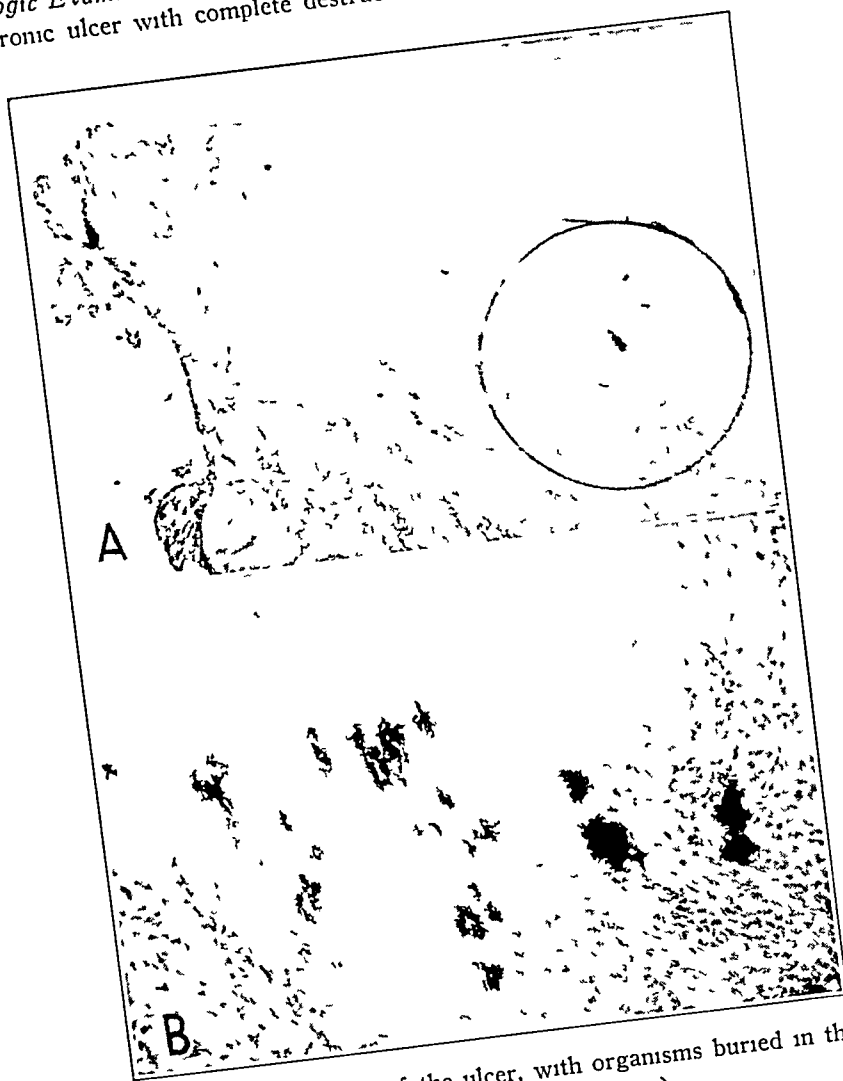


Fig 3 (case 3)—A, angle of the ulcer, with organisms buried in the granulation tissue. B, bacteria in the capillaries (Gram's stain).

ment by scar tissue. The eroded, sclerotic vessel lay at right angles to the surface. In the region of the rupture there was an acute inflammatory process involving the arterial wall and containing gram-positive cocci in clumps, suggestive of staphylococci (fig 4).

Sections taken at a distance from the point of hemorrhage showed malignant transformation of the epithelium; the architectural pattern of chronic ulcer was preserved.

Pathologic Diagnoses—The pathologic diagnoses were chronic pyloric ulcer with carcinomatous degeneration, acute infectious inflammation with erosion of the artery, and exsanguinating hemorrhage in the nonmalignant portion of the ulcer



Fig 4 (case 4) —*A*, acute infectious aneurysm of the artery in the base of in ulcer *B*, organisms seen in the region outlined in *A* (Gram's stain)

CASE 5—A white man apparently beyond the stated age of 56 was brought to the City Hospital after he had collapsed in the street. He was admitted to the surgical division, service of Dr. Frederick Bancroft, on March 24, 1939. Three months previously a right inguinal hernia had developed. For ten days the patient

had not eaten well because of loss of appetite, for seven days there had been no bowel movements, and for three days the hernia had been irreducible and painful and there had been vomiting. Operation was performed, and healing was normal. For a few days the temperature was slightly raised, and the patient became irrational and psychotic. Later he had sacral bed sores and appeared seriously ill, but no definite signs could be elicited to account for his general condition. On April 13, nineteen days after the operation, he vomited a large amount of blood and died suddenly.

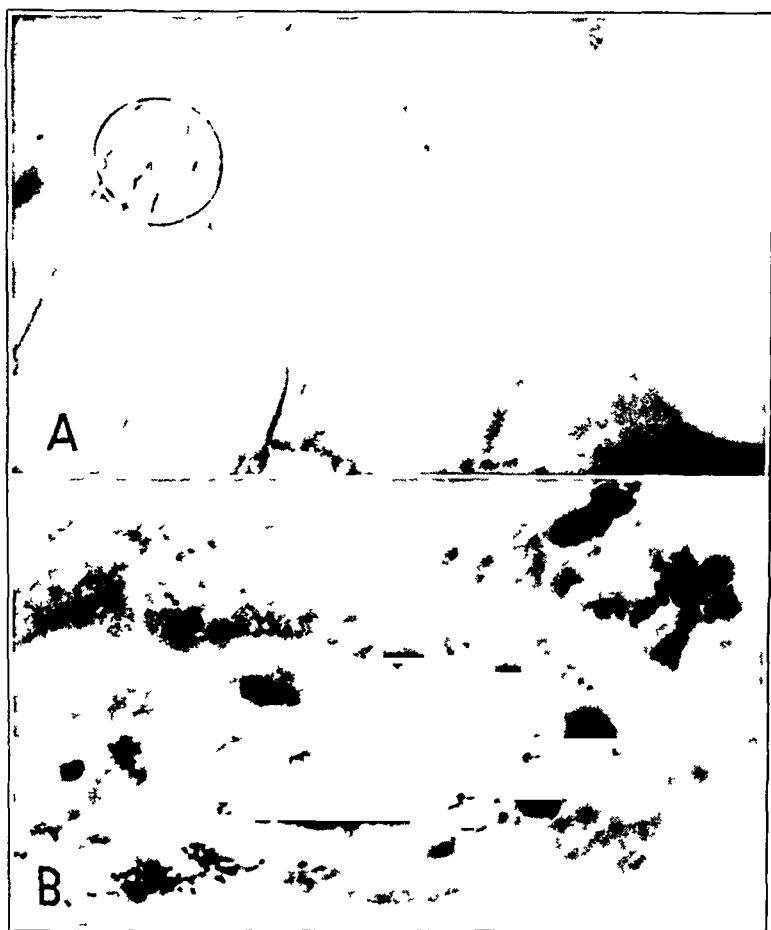


Fig 5 (case 5)—*A*, low power photomicrograph of the large open point of rupture. *B*, organisms observed in the masses of fibrin within the lumen of the vessel (Gram's stain)

Necropsy—The operative wound was healed. Clotted blood was present in the stomach and intestines. In the first portion of the duodenum, on the posterior wall, was a chronic ulcer measuring 3 by 2 by 2 cm, the base formed by the head of the pancreas. The surface was covered by an adherent blood clot which on removal revealed an eroded pancreaticoduodenal artery.

Histologic Examination—The tip of the eroded artery at the surface of the ulcer was involved in an acute necrotic process. Within the lumen of the vessel

and fairly deep in the course were masses of fibrin and numerous gram-positive organisms in clumps and chains (fig 5)

Pathologic Diagnoses—The pathologic diagnoses were chronic duodenal ulcer, acute infectious arterial aneurysm of the ulcer with rupture and exsanguinating hemorrhage, decubital ulcers of the sacrum, and hydronephrosis on the left with stones

COMMENT

Massive hemorrhage from chronic ulcer of the stomach or of the duodenum is one of the most serious accidents which can occur. In many instances its etiology is obscure. Crohn and Schwartzman¹ concluded that it is due to a local Schwartzman phenomenon from infections of other regions and particularly from acute diseases of the upper respiratory tract. They stated that in their opinion infection does not occur in the ulcer itself. The demonstration of bacteria has been reported occasionally in cases of acute ulcer in which death followed massive hemorrhage. Hartung and Warkany² reported the case of a 6 year old boy who died of hemorrhage from a duodenal ulcer during the course of meningococcic meningitis. Among other organisms seen in the base of the ulcer were gram-negative diplococci morphologically resembling *Neisseria*. In the series of causes of acute ulcer in children reported by Gerdine and Helmholtz³ there were several cases of hemorrhage in which bacteria were demonstrable. Sanford, Hughes and Weems⁴ reported an acute ulcer with hemorrhage and pneumococci in a case of pneumonia.

The seasonal incidence of recurrence of symptoms and of hemorrhages in ulcer is a well recognized phenomenon. Crohn and Schwartzman reported that an unusual number of patients having ulcers with hemorrhage were admitted to the Mount Sinai Hospital, New York, in February and March 1937, during a period of severe grippal infections. They stated that the same experience was encountered at Queens General Hospital, New York, at the same time. In the present series, 4 of the cases were observed in the winter months (December, February and March) and 1 in the spring (May).

The bacterial causative factor varied in the different cases, although the streptococcus was the most frequent organism. From antemortem

1 Crohn, B. B., and Schwartzman, G. Ulcer Recurrences Attributed to Upper Respiratory Tract Infection. A Possible Illustration of the Schwartzman Phenomenon, *Am J Digest Dis & Nutrition* **4** 705, 1938.

2 Hartung, C. A., and Warkany, J. Duodenal Ulcer as a Cause of Death in Meningococcal Meningitis, *J A M A* **110** 1101 (April 2) 1938.

3 Gerdine, L., and Helmholtz, H. F. Duodenal Ulcer in Infancy. An Infectious Disease, *Am J Dis Child* **10** 397 (Dec.) 1915.

4 Sanford, C. H., Hughes, J. D., and Weems, J. Pneumonia Complicated by Acute Pneumococcic Hemorrhagic Ulcerative Gastroenteritis (Dieulafoy's Erosion). Report of Two Cases, *Arch Int Med* **62** 597 (Oct.) 1938.

cultures of the blood, Friedlander's bacillus and hemolytic streptococci were isolated, and organisms of corresponding morphologic character were demonstrated at the point of hemorrhage. The other organisms observed could be judged only on the morphologic appearance. One was a definite chain coccus, another was of the streptococcus-pneumococcus group, and the third resembled a staphylococcus.

In most of the cases in our series the source of the infection was difficult to determine precisely. Only in case 2 was it clearly evident that the pneumonic process was the basis. The abscess with hemolytic streptococci found in the psoas muscle in case 3 seemed an unlikely source. It is more probable that septicemia from some other focus localized in two areas of previous damage, the abscess and the ulcer. In case 5 the decubital ulcer was the probable focus, the diseased kidney was a possible one, but its condition was "end stage" rather than active. In the other 2 cases the sources were entirely obscure.

The findings in this series offer a striking parallel to the production of acute ulcers by bacteria. Gerdine and Helmholtz³ stressed the bacterial origin of ulcer, particularly in children. Harkins⁵ showed that infected burns are prone to ulcerate and cited several observers who related sepsis and ulcer. We can draw no conclusion from our series in regard to the etiology of ulcer, but it seems reasonable to believe that in the presence of a transient bacteremia a chronic ulcer offers a favorable site for the localization of organisms and the production of an infectious process leading to rupture of vessels with resulting severe hemorrhage. They also suggest another avenue of preventive therapy in cases of recurrent hemorrhage, i. e., the search for and eradication of foci of chronic infection.

SUMMARY AND CONCLUSIONS

Five cases of chronic gastric and duodenal ulcer with death from exsanguinating hemorrhage are reported. A bacterial cause for the hemorrhage was demonstrated in each case. Cultures of blood in 2 cases yielded bacteria. The source of infection in 1 instance was the lung, in the others it was obscure. The suggestion is advanced that eradication of foci of chronic infection may be a preventive measure of value in cases of recurrent hemorrhage in chronic ulcer.

⁵ Harkins, H. N. Acute Ulcer of Duodenum (Curling's Ulcer) as Complication of Burns. Relation to Sepsis, Report of Case with Study of One Hundred and Seven Cases Collected from the Literature, Ninety-Four with Necropsy, Thirteen with Recovery, Experimental Studies, Surgery **3** 608, 1938.

CEREBRAL COMPLICATIONS FOLLOWING SURGICAL OPERATION

ETIOLOGY AND PATHOLOGY

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AND

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Postoperative complications of many types have long commanded the respectful attention of surgeons. Among the most serious, and the least well understood, are those which affect the central nervous system. Motor paralysis occurring in persons of the older age groups after operations have long been considered a coincidental accident having no direct connection with the operation. Such complications in younger persons have usually been looked on as the result of embolism from the operative site. Sudden death during or immediately after operation has been ascribed to cerebral embolism or to individual idiosyncrasy to the anesthetic. Prolonged coma, convulsions or psychic disturbances occurring during or shortly after operation have been commonly considered the result of the toxic effects of the anesthetic or of the "toxemia" arising from the condition requiring operation.

In this paper we wish to show that the cerebral complications of various types encountered after surgical operation may be the result of cerebral anoxia resulting from acute general circulatory collapse precipitated by the administration of an anesthetic, plus the trauma of operation, in persons whose margin of circulatory reserve has been reduced by a masked chronic circulatory insufficiency.

Our investigations indicate that so-called postoperative cerebral embolism is extremely uncommon. Cerebral complications are encountered, however, even in the best regulated clinics,¹ and we are able to show that in a large city hospital they are not rare. One of us (H E R) has had the opportunity to examine the brain and viscera in 21 cases in which the patients died after operation at the Philadelphia General Hospital. In each case symptoms referable to the cerebrum complicated the postoperative course.

From the Department of Thoracic Surgery and the Laboratory of Neuro-pathology, Philadelphia General Hospital.

Read before the Section on Surgery, General and Abdominal, at the Ninetieth Annual Session of the American Medical Association, St. Louis, May 17, 1939.

1 Woltman, H. W. Postoperative Neurologic Complications, in *Collected Papers of the Mayo Clinic and the Mayo Foundation*, Philadelphia, W. B. Saunders Company, 1937, vol. 29, pp. 712-722.

TYPE OF MATERIAL

The 21 cases comprising material for this study came from the several surgical services of a large city hospital. Preoperatively only 6 patients (28 per cent) could be considered poor surgical or anesthetic risks. There were 4 mid thigh amputations for gangrene, a splenectomy for hemolytic anemia and an exploratory laparotomy for intestinal obstruction.

The average age of the 21 patients was 38 years, and only 4 patients (19 per cent) were over 50 years of age (fig 1).

The operations included celiotomy (12 cases), operations on the femur (5 cases), obstetric anesthesia (2 cases), dilatation and evacuation of the uterus (1 case) and incision of a paronychia (1 case).

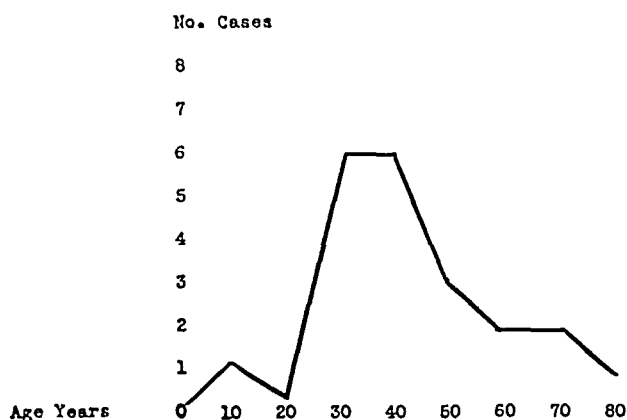


Fig 1—Age incidence of postoperative cerebral complications (21 cases)

The anesthetics used were as follows: ether, 12 cases, cyclopropane, 4 cases, nitrogen monoxide, 3 cases, and procaine hydrochloride, for spinal anesthesia, 2 cases.

SYMPTOMS

The very diversity of symptoms heretofore noted by other observers is a strong argument against the theory of cerebral vascular accident. In our series of 21 cases the symptoms were usually those suggesting diffuse involvement of the entire brain, and as a rule, at some period more than one symptom was present in each case.

The following symptoms of cerebral dysfunction were noted in our series:

Death during operation	3 cases
Psychic disturbances	3 cases
Prolonged coma (twelve to twenty-four hours)	5 cases
Generalized convulsions	5 cases
Focal cerebral symptoms (paralyses)	5 cases

Four patients with focal cerebral symptoms were under 33 years of age. The fifth, aged 61, had shown transient weakness of the right side of the body for nine days prior to operation, complete paralysis developing within twenty-four hours after operation.

Convulsions and prolonged coma may be observed while the patient is in the operating room. Psychotic manifestations may become apparent within a few hours after consciousness returns or may be noticed after several days. In 2 cases (not included in this series) we have observed psychoses which developed within forty-eight hours of operation to disappear completely, only to be followed by hemiplegia on the fifth postoperative day in 1 case and on the seventh in another. Both the patients died. Fourteen (76 per cent) of the patients in our series surviving longer than twelve hours died with hyperpyrexia unexplainable on an infectious basis.

ETIOLOGY AND PATHOLOGY

Ornstein² has briefly reviewed the controversy over the origin of postoperative focal cerebral symptoms which occurred during the latter half of the last century. His report shows that neurologists and pathologists had to devise various ingenious routes to carry thrombi from the major venous circulation to the cerebral arterial system. While it is probable that in a few postoperative cerebral accidents the cause may be found to be embolism, thrombosis affecting the end arteries or cerebral hemorrhage, evidence is accumulating which indicates that another factor is more often involved.

Recently, Courville³ has made the important suggestion that anoxia may account for the clinical and pathologic picture in cases of postoperative cerebral involvement. Since in all his cases⁴ nitrogen monoxide was the anesthetic, he felt that there was a direct relation between the asphyxia associated with this anesthetic and the cerebral anoxemia. He concluded that the anoxemia must result from a sudden circulatory or respiratory failure during the anesthetic period or must be due to the effects of oxygen want incident to prolonged nitrogen monoxide anesthesia.

2 Ornstein, A. M. Hemiplegia Following Childbirth and Pelvic Operations, *Arch Neurol & Psychiat* **5** 353 (March) 1921.

3 Courville, C. B. Asphyxia Following Nitrous Oxide Anesthesia, *Medicine* **15** 1129 (May) 1936, Pathogenesis of Necrosis of Cerebral Gray Matter Following Nitrous Oxide Anesthesia, *Ann Surg* **107** 371 (March) 1938.

4 Stewart, J. D., and Rourke, G. M. Changes in Blood and Interstitial Fluid Resulting from Surgical Operation and Ether Anesthesia, *J Clin Investigation* **17** 413 (July) 1938.

Gross inspection of the brain in our series lent no support to the theory of infarction as a result of embolism. Histologically⁵ we were able to confirm Courville's theory of widespread cellular degeneration throughout the brain, regardless of the type of clinical manifestation of cerebral involvement. In every case there was generalized capillary damage with widespread parenchymatous degeneration due to pericellular and interstitial edema. Although the edema due to capillary damage was universal, the cellular degeneration was most marked in the association areas of the cortex, the sympathetic ganglions in the gray matter around the third and fourth ventricles and lenticular nucleus, the dentate and

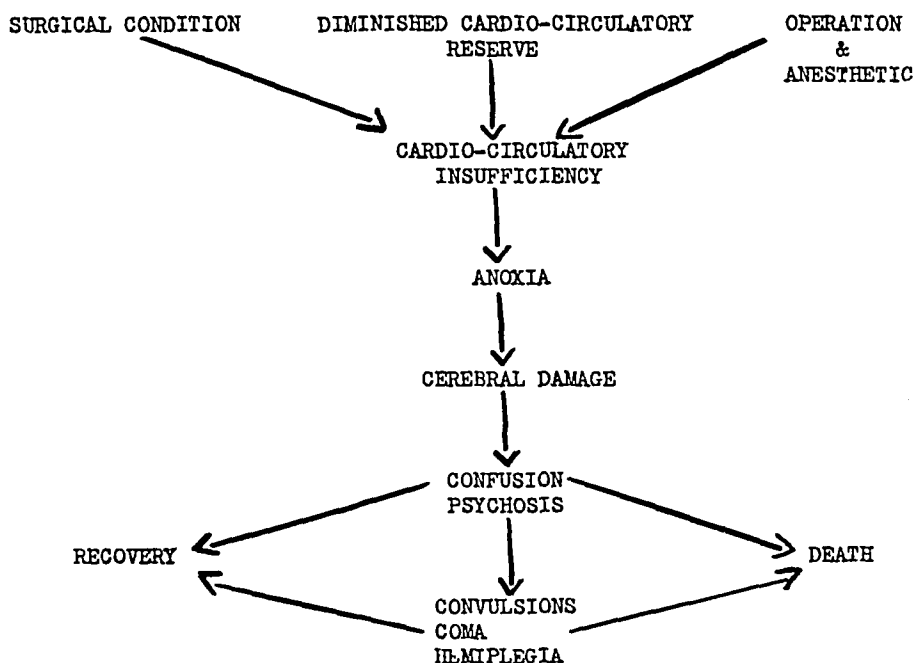


Fig 2—Pathogenesis and mechanism of postoperative cerebral complications

Purkinje cells of the cerebellum and the region of the inferior olive in the medulla. Since these are the areas that Chornyak⁶ has found most

5 The stain used on all sections is a trichrome stain developed by Miss Edna Beyer, technical assistant in neuropathology, laboratory of neuropathology, Philadelphia General Hospital. All forms of connective tissue and collagen stain blue, parenchymatous tissue and muscles stain red. In degenerative conditions muscles and parenchymatous cells are increasingly basophilic. By means of this stain it is possible to differentiate acute degenerative changes from those which are more chronic.

6 Chornyak, J. Structural Changes Produced in the Human Brain by Oxygen Deprivation (Anoxemia) and Their Pathogenesis, Ann Arbor, Mich., Edwards Brothers, Inc., 1938.

severely affected in animals subjected to atmospheres deficient in oxygen, this would further suggest that Courville's theory of asphyxia as a factor in the production of cerebral symptoms after anesthesia might be extended to include not only nitrogen monoxide anesthesia but all forms of anesthesia

Patients who survived less than forty-eight hours⁷ showed no evidence of reaction indicating attempted repair. In 8 of the 10 patients

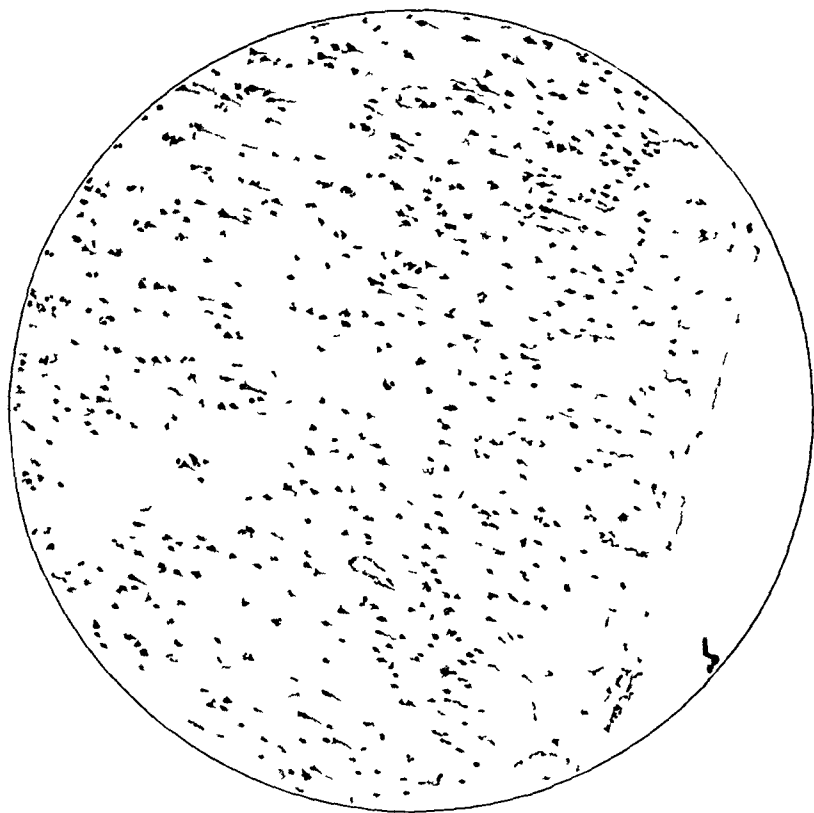


Fig 3—Section of the cerebral cortex ($\times 57$, toluidine blue stain). The patient died within twelve hours after the operation. There were widespread degenerative changes in the ganglion cells. There was local loss of cells in layers 3 and 4 (Brodmann). Note the patent cortical arteriole.

who survived from two to nine days there were focal areas of glial and phagocytic activity, suggesting beginning repair and scar formation.

Only 2 patients had a history of sudden temporary cardiac or respiratory failure during operation. In none of our cases was the period of anesthesia unusually long. Operation was performed on 3

⁷ McAllister, F. F. The Effect of Ether Anesthesia on the Volume of Plasma and Extracellular Fluid, *Am J Physiol* **124**: 391 (Nov.) 1938.

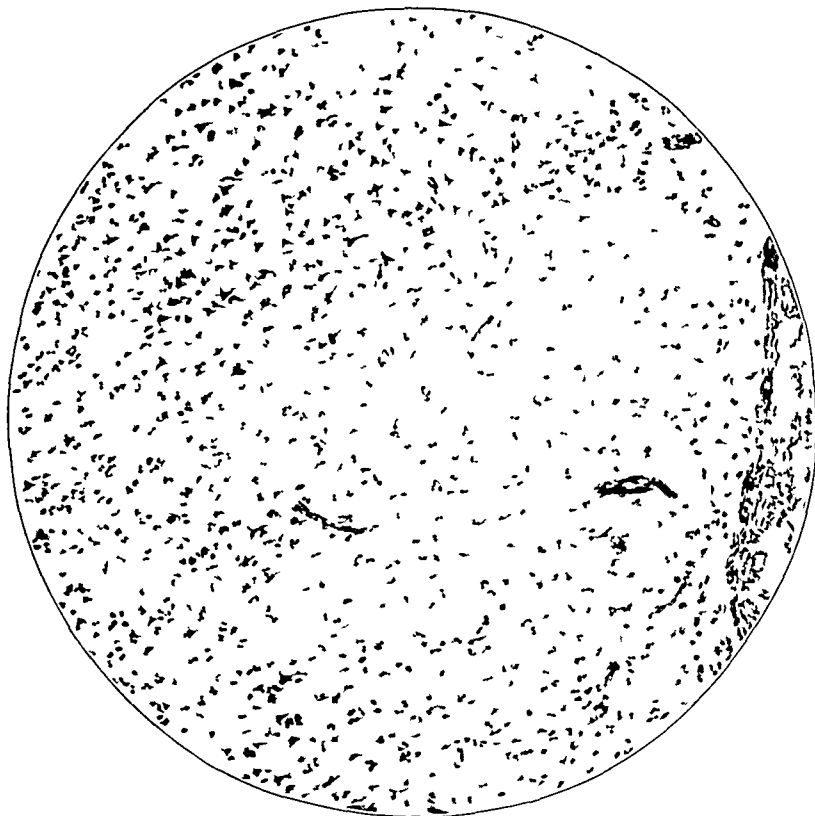


Fig 4—Section of the cerebral cortex ($\times 57$, toluidine blue stain) Delayed death occurred after a surgical operation There was a focal area of loss of ganglion cells, with proliferation of astrocytes and microglia (necrobiosis) The remaining ganglion cells showed severe ischemic degeneration Note the patent vessels with progressive alteration in their walls

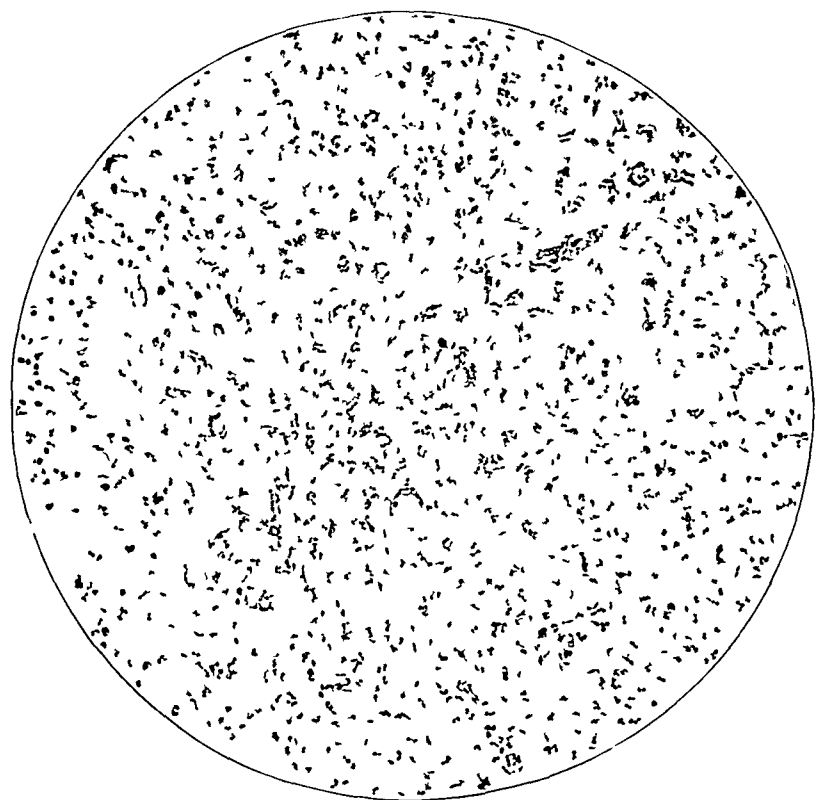


Fig 5—Section of the cerebral cortex ($\times 57$, toluidine blue stain) Delayed death occurred after a surgical operation There was total loss of ganglion cells, with proliferation of astrocytes and microglia Note the patent blood vessels

patients under light, brief nitrogen monoxide anesthesia, and in 2 cases inhalation anesthesia was not used, spinal anesthesia being substituted. In other words, it was observed that cerebral symptoms might follow the use of any type of anesthetic agent and were not related to the duration of anesthesia or to accidents occurring during the period of anesthesia. This suggested that we were dealing with some factor contributing to cerebral anoxia which was unrelated to the surgical status or to the anesthetic itself.

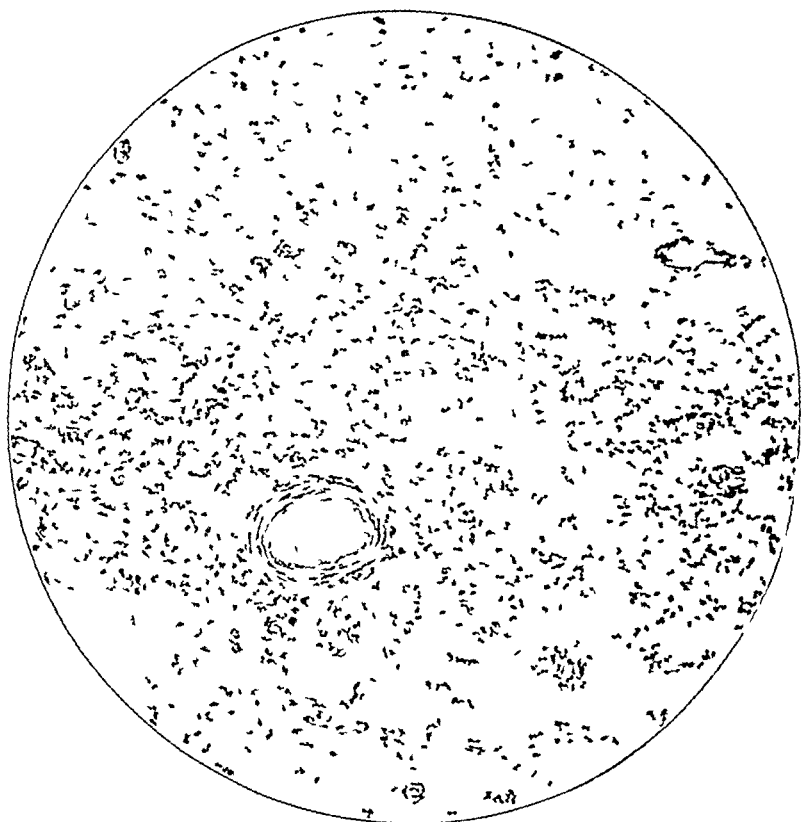


Fig 6—Section of the cerebral cortex ($\times 57$, toluidine blue stain). Delayed death occurred after a surgical operation. Note the local area of encephalomalacia. Masses of phagocytic cells surrounded the patent artery.

In view of the fact that edema and congestion not only of the brain but of the viscera were observed at autopsy, it would seem that the cerebral degeneration is more reasonably attributable to the combined effect of anesthesia and operation on general circulatory efficiency with secondary reflection in the brain than to a direct selective anoxia of the brain cells alone. The predominance of cerebral symptoms might be explained clinically by the fact that evidence of cerebral dysfunction is frequently so dramatic as to obscure the accompanying signs of dis-

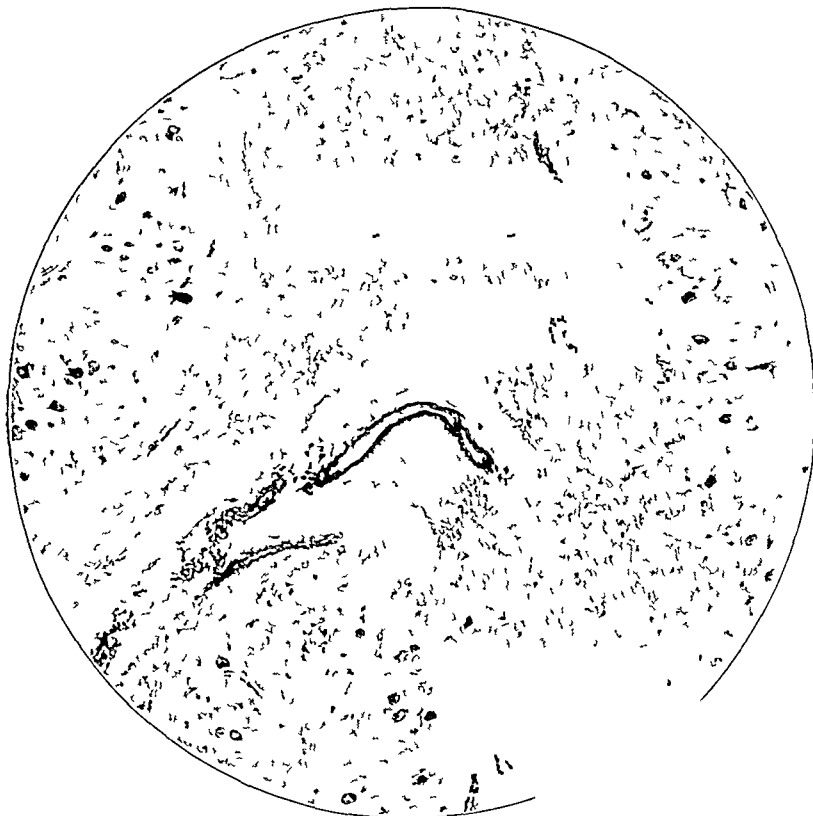


Fig 7—Section of the medulla in the region of the inferior olive ($\times 69$, trichrome stain) Death occurred during tonsillectomy The patient was a child aged 9 years Note the thickening and hyalinization of the walls of the blood vessel, which, with the perivascular degeneration, suggests cerebral circulatory insufficiency antedating the period of anesthesia

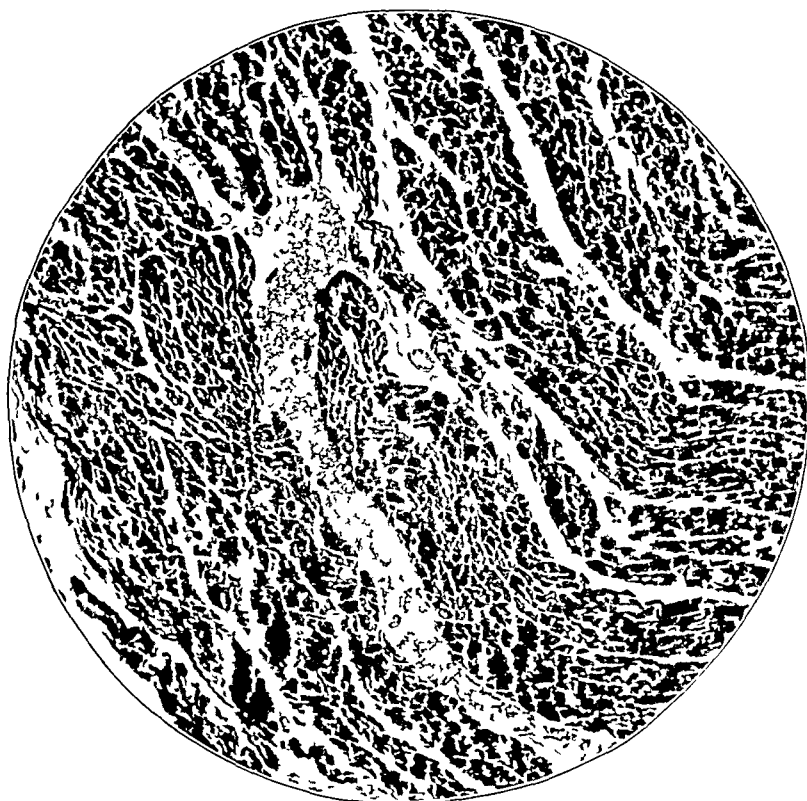


Fig 8—Section of the heart muscle ($\times 69$, trichrome stain) Death occurred during an operation performed with the patient under obstetric anesthesia The age of the patient was 27 There were intense dilatation and stasis in the venous radicles Edema of the tissue was present There was increase of interstitial connective tissue, suggesting preexisting circulatory stasis

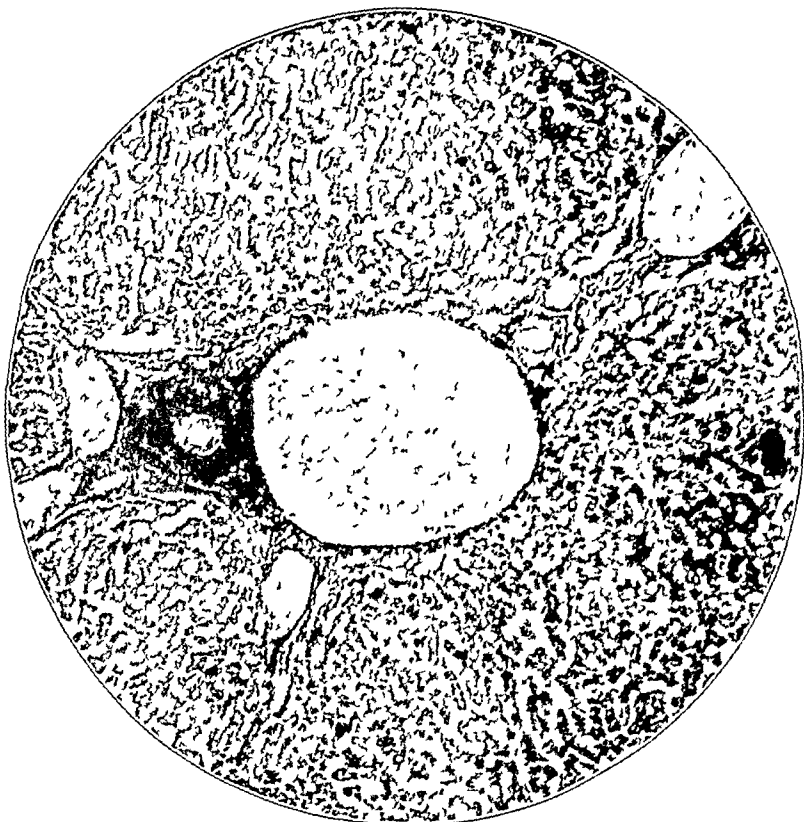


Fig 9—Section of the liver ($\times 69$, trichrome stain) Death occurred during an operation performed with the patient under obstetric anesthesia The age of the patient was 21 There was acute stasis indicated by hepatic sinusoids packed with red cells Note the increase of connective tissue around the bile duct, indicating preexisting circulatory insufficiency

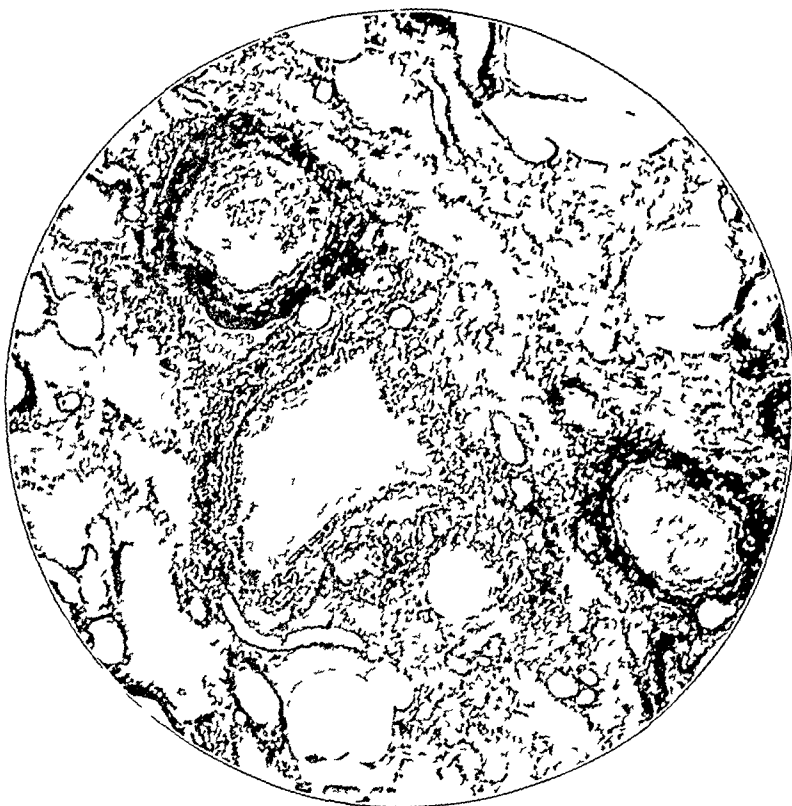


Fig 10—Section of the lung ($\times 69$, trichrome stain) Death occurred during an operation performed with the use of spinal anesthesia The age of the patient was 33 There was pulmonary edema as evidence of acute stasis Perivascular fibrosis was present, suggesting preexisting circulatory insufficiency

orders of visceral function Physiologically, the effect of general circulatory insufficiency is most evident in the brain because of the effect of the closed box of the skull on the increased volume of the brain (due to circulatory stasis) and because of the high metabolic rate and oxygen requirements of cerebral tissue

ROLE OF THE ANESTHETIC

While we have been able to demonstrate that death following anesthesia is the result of a generalized circulatory insufficiency in which cerebral symptoms dominate the clinical picture, it has not been established whether the anesthetic is the causative agent or merely the precipitating factor Regardless of the anesthetic agent employed, the cerebral lesions in our 21 cases were essentially the same, although the intensity of the process varied even with the same anesthetic

Experimentally, recent studies give a basis for the hypothesis that anesthesia alone may produce alterations in general circulatory efficiency Harrison⁸ has adequately demonstrated that a fall in blood pressure frequently occurs during spinal anesthesia

Using ether as the anesthetic, Boyce and McFetridge⁹ have shown a marked decrease in hepatic function, and Snyder,¹⁰ using the same agent, has shown that there are a 41 per cent drop in cardiac output and a decline in blood pressure Stewart and Rourke⁴ have reported a 15 per cent loss in circulating blood volume, while Bollman, Svirbely and Mann¹¹ have noted hemoconcentration to occur coincidentally with ether anesthesia in experimental animals In addition, McAllister⁷ has reported an 11 per cent decrease in plasma volume

It has been considered that such alterations in circulatory efficiency are transient Moon¹² stated that in the experimental animal complete anesthesia per se is rarely sufficient to produce failure of the circulation However, he cited war experience to show that anesthesia may precipitate circulatory failure (shock) under conditions in which circulation is already impaired

8 Harrison, T R Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1935

9 Boyce, F F, and McFetridge, E M Studies of Hepatic Function by the Quick Hippuric Acid Test, Arch Surg **37** 401 (Sept) 1938

10 Snyder, J C The Cardiac Output and Oxygen Consumption of Nine Surgical Patients Before and After Operation, J Clin Investigation **17** 571 (Sept) 1938

11 Bollman, J L, Svirbely, J L, and Mann, F C Blood Concentration Influenced by Ether and Amytal Anesthesia, Surgery **4** 881 (Dec) 1938

12 Moon, V H Shock Its Mechanism and Pathology, Arch Path **24** 642 (Nov), 794 (Dec) 1937

This is in line with Ravdin and Johnston's¹³ suggestion that the cumulative effects of oxygen deficit from impaired blood flow prior to anesthesia may be a factor in the production of a breakdown of normal function after surgical operation. The brain was first investigated to rule out the possibility of a circulatory factor operating locally. In this examination we studied only patients who were too young for the degenerative changes of middle life and who died within twenty-four hours after operation. In these cases, of which there were 9, we were able to demonstrate that there had been chronic circulatory insufficiency in the brain prior to induction of the surgical procedure. This was concluded on the basis of increased connective tissue around the blood vessels and in the subarachnoid space, on the presence of severe degenerative changes in the myelin sheath and particularly on the basis of perivascular demyelination. We were unable to show any local factor, such as occlusive atheromatous changes in the blood vessels, which might be responsible for local circulatory insufficiency.

From the clinical studies there is no suggestion that cardiovascular decompensation was present in any case. Nevertheless, studies of the viscera in the subgroup of young patients showed evidence of a similar process of circulatory insufficiency in all the viscera. These changes were in the nature of a parenchymatous change in the cells and an increase in connective tissue. In our entire series, although there had been no evidence of decompensation, we were able to show structural changes in the cardiovascular system which pointed to the fact that the patients had a reduced margin of circulatory efficiency.

ROLE OF LATENT CARDIOCIRCULATORY INSUFFICIENCY

This suggests that there are many cases in which there exists a latent cardiocirculatory insufficiency which under ordinary circumstances gives no clinical evidence of its presence. We are not concerned here with the possible and unavoidable "anesthetic death" which follows acute circulatory disturbances of the shock picture incident to severe trauma, abdominal catastrophes or peritonitis. We are concerned with the type of case in which there is a latent circulatory insufficiency which with the added stress of anesthesia and an acute condition requiring surgical intervention precipitates cerebral changes. Such changes are the more tragic because they are unexpected. Prior to operation the patient mentions no history or symptoms of cardiovascular disease, and when collapse is precipitated by the anesthetic, its circulatory origin is masked by the dominance of the cerebral symptoms. Such accidents can probably occur in the presence of a normal cardiocirculatory system, but in every case in our series we were able to establish a masked or

13 Ravdin, I. S., and Johnston, C. G. Nitrous Oxide Oxygen Anesthesia and Anoxia, *Am J M Sc* **194** 279 (Aug) 1937

latent chronic circulatory insufficiency as the basis for death. The underlying causes of reduced circulatory efficiency were varied. In 6 patients cardiac hypertrophy was present (average age, 41 years), and in 6 chronic myocardial degeneration was observed (average age, 30 years). Other factors were severe secondary anemia, rheumatic valvulitis (3 cases) and old cardiac infarct (2 cases).

SUMMARY

Twenty-one cases of postoperative cerebral complications have been studied, special attention being given to the condition for which the operation was performed, the operative risk, the age of the patient and the type of anesthetic used. The postoperative cerebral symptoms are enumerated. The etiology and pathology of cerebral complications are discussed, as are the parts played by the anesthetic and by the cardio-circulatory system.

The limitations of space render impossible at this time the discussion of the predisposing causes of postoperative cerebral accidents, their prevention and their treatment. These will be considered in future articles, as will the results of experimental animal investigations.

A brief abstract of each case is appended.

CONCLUSIONS

- 1 Cerebral complications following surgical operation are not rare.
- 2 Such complications are seldom the result of embolism or hemorrhage.
- 3 The cerebral lesion is usually diffuse, involving the entire brain.
- 4 Examination of the brain and other viscera reveals that cardio-circulatory efficiency usually has been impaired long before the operation is performed. This impairment is manifested chiefly by parenchymatous edema and congestion and by perivascular fibrosis. The presence of diminished circulatory efficiency is usually unsuspected.
- 5 Any anesthetic agent may contribute to the production of post-operative cerebral complications.
- 6 Cerebral complications (psychoses, coma, convulsions, paralysis) after surgical operation are frequently the sequels of relative cerebral anoxia produced by an alteration in blood pressure occurring as a result of the effect of surgical operation and of the anesthetic on a patient with impaired cardiocirculatory efficiency.

REVIEW OF CASES

Brief abstracts of the histories of the cases comprising this series are presented. In every case the brain showed widespread degenerative changes dependent on the effects of acute anoxia. There was also

evidence of a chronic circulatory insufficiency as manifested by perivascular demyelination and perivascular fibrosis. Factors we consider as predisposing to latent cardiocirculatory insufficiency are enumerated under the postmortem observations in each case.

CASE 1—J. G., aged 9, was admitted to the service of Dr. E. L. Eliason. On admission there was extreme tenderness in the right lower quadrant of the abdomen. Operation was done March 2, 1936, with nitrogen monoxide, oxygen and ether anesthesia. There was no evidence of peritonitis, but the appendix was bound down under the liver as a result of nonrotation of the cecum. Appendicostomy was performed. On March 3 the patient was restless and irrational. Death occurred the same day, the temperature being 108 F. fifteen hours after operation.

Postmortem Study—Cultures of blood from the heart and material from the peritoneal cavity were sterile. The kidneys showed bilateral hydronephrosis. The liver showed fatty infiltration. There was hypoplasia of the circle of Willis.

CASE 2—Miss R. H., a Negress aged 20, was admitted to the hospital from the service of Dr. John McGlinn. She was a primipara and had been followed in the "prenatal clinic" for five months before her admission Feb. 19, 1936, in labor. The blood pressure was 115 systolic and 70 diastolic. Low application of a Simpson forceps was done with the patient under nitrogen monoxide and oxygen anesthesia. There was moderate bleeding. The placenta was manually removed. The uterus was packed. The patient went into circulatory collapse shortly thereafter and did not recover.

Postmortem Study—The postmortem diagnosis was sickle cell anemia.

CASE 3—Miss A. G., white, aged 25, was transferred to the service of Dr. E. L. Eliason. She was admitted to the hospital Feb. 11, 1938, because of jaundice. The blood pressure was 118 systolic and 40 diastolic. The erythrocyte count was 1,200,000 and the leukocyte count, 4,200 per cubic millimeter of blood. The volume index was 11. The Kahn reaction was 4 plus. The medical diagnosis was hemolytic anemia. On March 26 splenectomy was performed because of splenomegaly. Cyclopropane anesthesia was employed. Left hemiplegia was noted on March 30, and the patient died April 4 with a temperature of 104 F.

Postmortem Study—The brain showed an anomalous circle of Willis. There was severe hemolytic anemia.

CASE 4—Mrs. M. K., a Negress aged 27, in the service of Dr. Frank Hammond was admitted to the hospital Oct. 22, 1934. The past history was irrelevant. Physical examination revealed no abnormality. The blood pressure was 100 systolic and 65 diastolic. The Kahn reaction was negative. On October 24 a perineorrhaphy and a bilateral salpingectomy were performed with the patient under nitrogen monoxide, oxygen and ether anesthesia. On October 24 clinical evidence of shock (coma) was noted. On October 30 there were confusion and convulsions. After this the patient was confused and incontinent until death, which occurred on November 2 with a temperature of 103 F.

Postmortem Study—The heart showed chronic rheumatic valvulitis. The liver showed fatty degeneration.

CASE 5—Mr. A. D., white, aged 27, was transferred to the service of Dr. Harvey Righter. He was admitted June 22, 1934, to the psychopathic department. He was

chronically alcoholic The symptoms and the blood picture were suggestive of hyperinsulinism The electrocardiogram showed myocardial weakness The blood pressure was 100 systolic and 60 diastolic Nitrogen monoxide, oxygen and ether anesthesia was used No definite tumor was found, but the tail of the pancreas was resected Postoperative shock (coma) was noted He died September 4 with a temperature of 108 F

Postmortem Study—The heart showed hypertrophy with severe degeneration The liver showed fatty infiltration

CASE 6—Mrs A J, a Negress aged 28, was a patient in the service of Dr Frank Hammond She had attended the "prenatal clinic" and was admitted to the hospital in labor on Nov 2, 1935 She was a primipara and was obese Sugar was observed in the urine at various times ante partum The Wassermann reaction of the blood was 4 plus The blood pressure was 176 systolic and 100 diastolic During induction of anesthesia with nitrogen monoxide and oxygen she suddenly stopped breathing and could not be revived The child was not delivered

Postmortem Study—The heart showed cardiac hypertrophy The brain showed a hypoplastic circle of Willis

CASE 7—Mrs L O, a Negress aged 28, in the service of Dr Hubley Owen, was admitted to the hospital March 15, 1935 She had taken salts on March 12 The blood pressure was 140 systolic and 75 diastolic Appendectomy and drainage of an appendical abscess were done on March 15 with the patient under nitrogen monoxide, oxygen and ether anesthesia There were convulsions for four days before death The patient died March 20, with a temperature of 108 F

Postmortem Study—There was a well walled-off pelvic abscess The heart showed severe myocardial degeneration with atheroma of the aorta The liver showed hemosiderosis The lungs showed atelectasis

CASE 8—Mrs E C, a Negress aged 31, in the service of Dr Frank Hammond, was admitted to the hospital on Nov 13, 1934 There was a history of occasional dyspnea on exertion and dizziness The blood pressure was 120 systolic and 80 diastolic Cardiac examination gave negative results Slight pitting edema of the ankles was present The Kahn reaction was negative Operation (hysterectomy and appendectomy) was performed November 15 with nitrogen monoxide, oxygen and ether anesthesia The immediate reaction was good, but several hours later shock (coma) was noted The patient died November 16

Postmortem Study—There was a moderate secondary hemorrhage (1 liter) in the pelvis The heart was hypoplastic and showed severe myocardial degeneration

CASE 9—Dr W V, a white man aged 32, in the service of Dr J O Bower, Dr P McCarthy and Dr J R Moore, was admitted to the hospital April 20, 1933, with fracture of both femurs following an automobile accident After open reduction both femurs were involved by chronic osteomyelitis Thirteen operations were subsequently performed After the last operation, performed Sept 13, 1936 with spinal anesthesia, the patient showed evidence of shock Right hemiplegia was noted The patient died October 3

Postmortem Study—There was atrophy of the iliac arteries and veins, with a recanalized thrombus of the inferior vena cava The aorta showed a partially organized mural thrombus The brain showed an anomalous circle of Willis

CASE 10—Mr W C, a Negro aged 33, in the service of Dr Louis Englerth, was admitted to the hospital July 1, 1935. He had been a typhoid carrier since 1933. The blood pressure was 105 systolic and 70 diastolic. Cardiac examination gave negative results. The urine gave a 2 plus reaction for albumin. The Kahn reaction was negative. Cholecystectomy was performed July 3. Procaine hydrochloride (spinal) anesthesia was used. The blood pressure was 180 systolic and 120 diastolic. After administration of the anesthetic and during the operation the blood pressure fell rapidly and the respirations became shallow, ceasing twenty minutes after the anesthetic was given. Artificial respiration and intravenous dextrose were used, but to no avail.

Postmortem Study—The heart showed concentric hypertrophy of the left ventricle.

CASE 11—Mr L L, white, aged 33, in the service of Dr Louis Englerth, was admitted to the hospital Oct 12, 1935. There was a history of pain in the right side since December 1. The patient was markedly obese. The urine gave a 3 plus reaction for albumin and contained sugar. The blood pressure was 145 systolic and 95 diastolic. Operation (appendectomy for a gangrenous ruptured appendix) was performed December 10, with nitrogen monoxide, oxygen and ether anesthesia. On December 11 the patient was stuporous. Weakness was noted on the right side. He died December 12, with a temperature of 105 F.

Postmortem Study—The heart showed hypertrophy. The liver showed fatty degeneration. The brain showed a hypoplastic circle of Willis.

CASE 12—Mrs J W, a Negress aged 33, in the service of Dr Harvey Richter, was admitted to the hospital March 6, 1929, for an incomplete abortion. There had been profuse bleeding from March 3 until admission. Edema of the ankles and palpitation had been noted during pregnancy. The heart was enlarged, the rhythm was irregular. The blood pressure was 160 systolic and 90 diastolic. The Kahn reaction was 4 plus. Dilation and evacuation of the uterus were done with the patient under nitrogen monoxide anesthesia. She stopped breathing at the end of the operation, and artificial respiration was instituted. She recovered temporarily, but right hemiplegia and flaccidity of the extremities developed on March 20. She died March 23. The temperature at death was 107 F.

Postmortem Study—The liver showed fatty degeneration.

CASE 13—Mrs A K, white, aged 36, in the service of Dr P McCarthy, was admitted to the hospital Sept 17, 1935. The systolic blood pressure varied between 160 and 204, the diastolic pressure being 110. The clinical picture of the Cushing syndrome had been present for two years. Exploratory laparotomy was done November 1 for a possible tumor of the adrenal gland, cyclopropane anesthesia being employed. No tumor was found, but the left adrenal gland and the tail of the pancreas were removed. The patient responded poorly to the operation and died, apparently from shock, November 3.

Postmortem Study—The heart showed severe myocardial degeneration with fragmentation. The liver showed fatty degeneration. The kidneys showed nephrosclerosis.

CASE 14—Mrs E D, white, aged 42, in the service of Dr C A Behney, was admitted to the hospital Feb 18, 1936, because of uterine bleeding. The urine gave a 3 plus reaction for sugar and a 2 plus reaction for albumin. A hysterectomy, a bilateral salpingo-oophorectomy and an appendectomy were performed because of a fibroid tumor. The blood pressure was 208 systolic and 98 diastolic. The

erythrocyte count was 3,000,000 per cubic millimeter of blood. The Wassermann reaction of the blood was 4 plus. Ether anesthesia was used. The patient lived eighteen hours after the operation. She was irrational, and tonic spasms were noted. She died February 20 with a temperature of 104 F.

Postmortem Study—The heart showed a healed cardiac infarct.

CASE 15—Mrs. S. B. V., white, aged 43, in the service of Dr. Harvey Righter, was admitted to the hospital Aug. 12, 1926. There was a history of chronic glomerular nephritis, allergy to food and drugs and dyspnea on exertion for one year. Appendectomy was performed August 12, with nitrogen monoxide and oxygen anesthesia. The patient collapsed after the operation, while still in the operating room, and never recovered consciousness. She died August 14.

Postmortem Study—The heart showed hypoplasia.

CASE 16—Mrs. M. S., white, aged 49, in the service of Dr. E. L. Eliason, was admitted to the hospital March 22, 1936, because of weakness, dyspnea on exertion and pain in the right leg. Physical examination showed cardiac enlargement, mitral stenosis, auricular fibrillation and evidence of occlusion of the right femoral artery. The blood pressure was 170 systolic and 80 diastolic. The value for blood sugar was 163 mg. per hundred cubic centimeters. On April 1 a mid-thigh amputation was performed on the right, with nitrogen monoxide, oxygen and ether anesthesia. On April 2 the patient was mentally confused. She died April 3, with a temperature of 102 F.

Postmortem Study—The heart showed chronic rheumatic valvulitis.

CASE 17—Mrs. S. S., white, aged 53, was admitted to the hospital from the service of Dr. Harvey Righter. The past history was irrelevant. Cardiac examination gave negative results. The blood pressure was 134 systolic and 82 diastolic. On Aug. 11, 1934, incision and drainage were done for tenosynovitis of the fourth finger of the left hand. Nitrogen monoxide and oxygen anesthesia was used. Reoperation was performed September 4, with incision and drainage for tenosynovitis of the left hand. The same anesthetic was used. The patient stopped breathing during the operation and remained in coma for five hours. Thereafter she was irrational until death, which occurred September 7 with a temperature of 105 F.

Postmortem Study—The heart showed severe myocardial degeneration. The liver showed portal cirrhosis and fatty degeneration.

CASE 18—Mr. S. P., white, aged 57, was transferred to the service of Dr. E. L. Eliason. He was known to have had diabetes for four years. He was admitted to the hospital in stupor on Aug. 10, 1935. The value for blood sugar was 200 mg. per hundred cubic centimeters. The erythrocyte count was 2,920,000 per cubic millimeter, with 50 per cent hemoglobin. The leukocyte count was 8,100 per cubic millimeter. The carbon dioxide-combining power was 50 volumes per cent. The blood pressure was 130 systolic and 80 diastolic. On August 10 a mid-thigh amputation was done for an infected, gangrenous foot. The stump was left open. Cyclopropane anesthesia was used. Clonic movements were noted shortly after the operation. The patient died August 15 with a temperature of 106 F.

Postmortem Study—The heart showed calcified aortic and mitral valves with mitral stenosis. There was concentric hypertrophy. The liver showed early portal cirrhosis.

CASE 19—Mrs A S, white, aged 62, was transferred to the service of Dr Louis Englerth. She was admitted in coma to the metabolic department on Aug 16, 1937. There was transient weakness of the right side of the body nine days before admission. The blood pressure was 135 systolic and 35 diastolic. Infection of the right foot was noted. The coma responded to medical treatment. Amputation of the right leg at the midthigh was done on August 17, with cyclopropane anesthesia. Complete right hemiplegia was noted on August 19. The patient died on that day, with a temperature of 108 F.

Postmortem Study—The heart showed severe atheroma of the coronary arteries and aorta and hypertrophy. The kidneys showed acute pyelonephritis. The brain showed an anomalous circle of Willis.

CASE 20—Mrs E S, white, aged 65, was transferred to the service of Dr Louis Englerth. She was admitted to the hospital Aug 11, 1934. She was known to have had diabetes for eight years. The blood pressure on admission was 142 systolic and 62 diastolic. The value for hemoglobin was 60 per cent. The liver was palpable 6 cm below the costal border. The preoperative blood pressure was 90 systolic and 52 diastolic. Laparotomy was performed because of partial intestinal obstruction. Empyema of the gallbladder was found. Partial cholecystectomy was performed with nitrogen monoxide, oxygen and ether anesthesia. Postoperative twitching of the extremities was noted. Death occurred twelve hours after the operation.

Postmortem Study—The heart showed concentric hypertrophy with marked fibrosis of the myocardium. The brain showed the circle of Willis to be extremely hypoplastic.

CASE 21—Mrs R K, white, aged 70, in the service of Dr W W Babcock, was admitted to the hospital Nov 10, 1937. She was known to have had diabetes for five years. There was painful gangrene of the right leg. The blood pressure ranged between 166 and 182 systolic and 70 and 90 diastolic. There was a systolic aortic and mitral murmur. A midthigh amputation was performed Jan 1, 1938, with cyclopropane anesthesia. The patient showed confusion and catatonia. She died January 17 with a temperature of 102 F.

Postmortem Study—The heart showed a healed cardiac infarct. The liver revealed parenchymatous and fatty degeneration. The kidneys showed benign and malignant nephrosclerosis. The brain showed anomalies of the circle of Willis.

ABSTRACT OF DISCUSSION

DR HENRY K BEECHER, Boston. The questions raised by Dr Behrend and Dr Riggs are so controversial that it is not likely that they will be completely settled for a long time. Dr Behrend assigns a role of primary importance to preexisting latent circulatory impairment in the causation of neurologic complications. With that concept I must disagree. It is possible that that explanation accounts for the complications observed in some cases, although accumulation of convincing evidence on that score is difficult.

Patients who do not die at once of severe anoxia are bound to show considerable evidence of damage. For a certain period, at least, this evidence increases. The difficulties of distinguishing preexisting from postaccidental injuries increase with the length of time the patient survives after the accident.

Many more cases than have been reported by Drs Behrend and Riggs would be necessary to establish reasonable certainty of the significant presence of preexisting vascular lesions.

Most persons pass through a considerable period of anoxia before death occurs. Would it not be advisable, even necessary, to control the observations reported by an examination of pathologic material from patients who do not belong in this series, that is, by an examination of ordinary autopsy material to check the general frequency of evidences of old, latent circulatory impairment?

I should like to ask Dr. Behrend and Dr. Riggs why it is (if preexisting latent circulatory impairment is of such importance) that these neurologic complications do not occur with some regularity in patients with frank circulatory lesions. It is my observation that they do not customarily occur in patients with frank cardiac or circulatory defects.

Convulsions occurring during anesthesia are one of the most dramatic forms of complication. The single point on which everybody seems to be agreed concerning such convulsions is that they characteristically occur in children and in young adults. Surely it would not be contended that latent circulatory impairment is more common in this group.

In five years general anesthesia has been used in some 45,000 cases at the Massachusetts General Hospital. There have been nine convulsions in 8 patients. Roughly, one-half (25,000) of the patients were charity patients, 20,000 were private patients, 15,000 of these private patients were anesthetized by essentially the same staff and by the same technics as the charity patients, yet all of the convulsions occurred in the charity patients. There is no evidence, so far as I know, that such patients are more apt to have latent circulatory impairment than others.

I do not believe that one has any right to assign a greater importance to one suggested mechanism than to another. I agree with Dr. Behrend and Dr. Riggs that anoxia is a probable cause of these complications. The chief evidence for this is simple but indirect, it is known that anoxia does, on occasion, produce similar lesions. Little else is certain.

DR. F. H. LEWY, Philadelphia. I should like to mention one aspect of the mechanism of the phenomenon. It is a well known fact that "high-strung" persons are not good risks for narcosis. The good result of preoperative application of sedatives in preventing the operative shock suggests that the vasomotor nervous system may play a part in the conditions here described.

Anoxia of the brain cells, on the other hand, may be the direct consequence of angiospasm of the cerebral blood vessels or may follow peripheral vasomotor paralysis. I should like to ask whether the history or the results of examination of any of the patients of Dr. Behrend and Dr. Riggs suggested the presence of constitutional vasolability and whether the condition of the patients spoke more in favor of angiospasm or paralysis.

DR. ALBERT BEHREND, Philadelphia. It is essential for the surgeon to understand the importance of maintaining a supply of oxygen particularly to the brain but also specifically to the liver, kidneys and heart of a patient during and after an operative procedure. More and more surgery is becoming applied physiology. Ability to prevent many little understood postoperative complications involving the liver, kidneys, cardiovascular system and brain will depend on a better understanding of the physiology of these organs.

The patients in this series were all operated on in a city institution. In the cases of most of them cardiac and circulatory disorders were neither apparent nor suspected. I think that cerebral accidents occur in the presence of known cardiac and circulatory disease, but their relative infrequency may be attributed to the

fact that in such cases great care is taken to avoid complications during the period of operation. However, experienced clinicians all emphasize the difficulty of forecasting the response of a patient with cardiac disease to operation.

Dr Lewy has brought up a point of some importance. We have had a patient who showed evidence of a very labile neurocirculatory mechanism. The patient was a typhoid carrier admitted to the hospital for cholecystectomy. In the course of routine examination he showed a blood pressure of 110 mm of mercury systolic. Under the stress of preoperative anxiety his blood pressure rose to 160 mm of mercury systolic. He was then given a spinal anesthetic, and his blood pressure rapidly dropped, so that in forty minutes there was gradual slowing of the respiration and circulation and the patient died despite all efforts to restore him. Greater knowledge of the nervous control of the circulatory system may help to explain postoperative shock in some cases.

TISSUE METABOLISM AND PHOSPHATASE ACTIVITY IN EARLY CALLUS

J P TOLLMAN, M D
OMAHA

D H DRUMMOND, M D
DAYTON, OHIO

AND

A R McINTYRE, M D

AND

J DEWEY BISGARD, M D
OMAHA

In 1930, Kay¹ observed a rise in the level of serum phosphatase following fracture and suggested that this might be on the basis of increased local production of phosphatase. McKeown and Ostergren² studied the phosphatase activity in healing fractures in albino rats. They found a rise in osseous phosphatase during callus formation and a fall during development of the medullary space. Peden³ followed the concentration of plasma phosphatase in healing fractures in children and found a rise during the first few days, followed by a fall. Gutman, Sproul and Gutman⁴ found increased phosphatase activity at the site of osteoplastic metastases secondary to carcinoma of the prostate. Botterell and King⁵ studied changes in callus and blood phosphatase in rabbits. They found an increase at the site of fracture which lasted fifty to sixty days. This was seen to be related to the degree of osteoblastic activity of the callus. They found no significant changes in the phosphatase content of the blood. Wilkins and Regen⁶ demonstrated

From the University of Nebraska College of Medicine

1 Kay, H D. Plasma Phosphatase. II. The Enzyme in Disease, Particularly in Bone Disease, *J Biol Chem* **89** 249, 1930

2 McKeown, R M, and Ostergren, J I. Phosphatase Content of Fractured Bone, *Proc Soc Exper Biol & Med* **29** 54-56, 1931

3 Peden, O D. Plasma Phosphatase and Phosphorus During Healing of Fractures in Children, *Arch Dis Childhood* **12** 87-90, 1937

4 Gutman, E B, Sproul, E E, and Gutman, A B. Significance of Increased Phosphatase Activity of Bone at the Site of Osteoplastic Metastases Secondary to Carcinoma of the Prostate, *Am J Cancer* **28** 485-494, 1936

5 Botterell, E H, and King, E J. Phosphatase in Fractures, *Lancet* **1** 1267-1270, 1935

6 Wilkins, W E, and Regen, E M. Course of Phosphatase Activity in Healing of Fractured Bones, *Proc Soc Exper Biol & Med* **32** 1373, 1935

increased phosphatase activity at the site of fractures in rabbits, associated with a slight increase in blood phosphatase. Hunsberger and Ferguson⁷ found a variable rise in values for blood phosphatase during repair of fractures. Roe and Whitmore⁸ have reported a number of cases in which increased phosphatase activity was associated with proliferation of bone. Woodard, Twombly and Bradley⁹ found increases in blood phosphatase in cases of bone tumor. They showed that the highest values were obtained in cases of osteogenic sarcoma. It is seen that local osseous proliferation is associated with increased local phosphatase activity and sometimes with increased values for blood phosphatase. It was felt that it would be of interest to study the relation between the phosphatase activity of the callus and its metabolic activity. Because of the necessity of using macerated tissue for the metabolic determinations, only early calluses could be used.

METHOD

Adult rabbits were used. With sterile technic the radius on one side was exposed and the periosteum separated and elevated. A portion of bone about 1 cm in length was removed. The incision was then closed with a silk suture. Immediately before operation blood was removed from the heart for determination of the phosphatase content. Since this work is concerned with tissues having a high phosphate content, a method of determination independent of phosphate blanks was chosen. The method of King and Armstrong¹⁰ is well adapted to this end. It was used for both tissue and blood. At progressive intervals of three to four days after operation 2 rabbits were roentgenographed and killed, and the callus was removed for study. Immediately after death blood was taken for determination of the phosphatase content. A small portion of the callus was reserved for microscopic study, and the remainder was weighed and macerated in Dixon-Ringer solution^{10a}. On this extract the oxygen consumption was measured by the method

7 Hunsberger, A., and Ferguson, L. K. Variations in Phosphatase and Inorganic Phosphorus in Serum During Fracture Repair, *Arch Surg* **24** 1052-1060 (June) 1932.

8 Roe, J. H., and Whitmore, R. Clinicopathologic Application of Serum Phosphatase Determination with Special Reference to Lesions of the Bones, *Am J Clin Path* **8** 233-254, 1938.

9 Woodard, H. O., Twombly, G. H., and Bradley, L. C. A Study of Serum Phosphatase in Bone Disease, *J Clin Investigation* **15** 193-201, 1936.

10 King, E. J., and Armstrong, A. R. A Convenient Method for Determining Serum and Bile Phosphatase Activity, *Canad M A J* **31** 376, 1934.

10a Dixon-Ringer solution is composed of the following ingredients: 100 cc of solution of sodium chloride (0.9 Gm per hundred cubic centimeters), 2 cc of solution of potassium chloride (1.19 Gm per hundred cubic centimeters), 2 cc of solution of calcium chloride (1.47 Gm per hundred cubic centimeters), 2 cc of 10 per cent dextrose.

The mixture was boiled for fifteen minutes, cooled in oxygen free from carbon dioxide, and made up to the original volume with water free from carbon dioxide.

of Warburg¹¹ The phosphatase was then extracted, the mixture being allowed to stand in the ice box for thirty-six hours and the supernatant fluid was used for determination of the value for tissue phosphatase Because of the small amount of tissue available, separate specimens could not be taken to determine the calcium content As the calcium studied was insoluble, however, it was felt to be sufficiently accurate to use the tissue residue from the extraction for this purpose Organic matter was removed by digestion with concentrated nitric acid, and the calcium content was determined by a modification of the method of Clark and Collip¹²

RESULTS

The results of this work are presented in table 1 The data are on a basis of the wet weight of the tissue with the exception of the oxygen consumption, which is expressed in a conventional manner, Q_{O_2} being

TABLE 1—*Tissue Metabolism and Phosphatase Activity in Early Callus*

Age of Fracture, Days	Sex of Animal	Blood Phosphatase		Weight of Callus, Mg	Phosphatase, Units/Gm	Q_{O_2} *	Calcium, Mg/Gm of Tissue
		Initial Value	Final Value				
4	F	3.1	2.4	144	153	-3.72	
4	F	4.3	9.2	165	154	-3.47	
7	F	6.2	2.0	65	216	-4.15	4.6
7	F	2.8	3.8	285	21	Failure	0.7
9	F	2.3	3.2	152	380	-6.80	3.3
9	F	5.6	3.9	182	1,050	-3.78	13.2
10	M	4.3	9.6	101	276	-1.75	5.9
10	F	1.8	6.1	65	154	-2.75	3.1
12	F	26.6	18.7	82	850	-2.55	9.8
12	F	23.8	12.6	105	3,480	-0.10	20.0
12	F	2.5	6.0	105	200	-0.20	8.6
12	F	6.1	4.0	144	550	-5.20	3.5

* Oxygen consumption in cubic millimeters per milligram of dry weight of tissue in one hour

the consumption of oxygen in cubic millimeters per milligram of dry weight of tissue per hour In tables 2 and 3 the changes in roentgen and microscopic appearance are outlined

There appeared to be a considerable variation in the values representing the metabolic rate, which was due to the inherent error of this type of determination plus individual variations in the callus There was on the average a falling off in metabolic activity as the age of the callus increased This must have been due to decreased activity of the tissues rather than to replacement by calcium, since the amount of calcification present in the early callus was not sufficient to affect materially the

11 Warburg, O Ueber die Rolle des Eisens in der Atmung des Seesgeleis nebst Bemerkungen über einige durch Eisen beschleunigten Oxidationen, *Ztschr f physiol Chem* **92** 231-256, 1914

12 Clark, E P, and Collip, J B Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, *J Biol Chem* **63** 461-464, 1925

amount of active tissue present. The results obtained here are in substantial agreement with those given by Neuhaus¹³

The degree of calcification showed a general increase with age of the callus, but this also showed some variability. This was due in part to the possibility of varying degrees of decalcification of the ends of

TABLE 2—*Roentgen Appearance of Healing Fractures*

Age of Fracture, Days	Roentgen Appearance
4	Sharp osteotomy defect; no callus; no decalcification of fragments
4	Similar to previous specimen, small bone chip present
7	Possible early decalcification of bone adjacent to osteotomy
7	Traumatic fracture of ulna; marked soft tissue swelling
9	Slight soft tissue swelling, early increased density throughout defect
9	Similar to previous specimen
10	Definite patchy calcium deposition in defect; some decalcification of fragments
10	Similar to previous specimen
12	Marked but somewhat patchy calcium deposition in osteotomy defect
12	Similar to previous specimen, but callus thicker and not limited to region of defect
12	Rather dense patchy calcification, but quantity much less than in previous two specimens
12	Slight patchy calcification

TABLE 3—*Microscopic Appearance of Healing Fractures**

Age of Fracture, Days	Tissue Elements
4	Fibroblasts, capillaries; small capillaries
4	Fibroblasts, fibrous tissue; relatively few vessels
7	Dense fibrous tissue; early calcification; osteoblastic differentiation
7	Fibrous tissue; early calcification, necrosis; cellular infiltration
9	Young bone spicules with fibrous tissue among them
9	Dense fibrous tissue; centers of early ossification
10	Extensive young bone formation
10	Dense fibrous tissue; early calcification
12	Dense fibrous tissue; early calcification
12	Extensive young bone formation
12	Fibrosis; slight calcification
12	Fibrosis; slight calcification

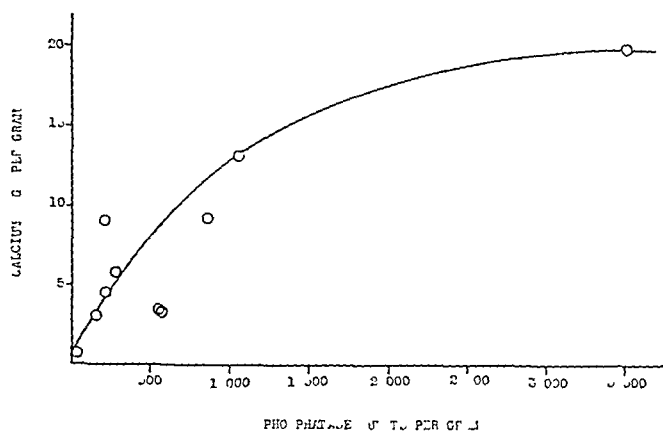
* In interpretation of the microscopic material it must be remembered that these sections may not all be representative because of the small amount of tissue available. The larger pieces were taken for metabolic studies.

the bone at either side of the osteotomy, also small bone chips or bone dust left in the osteotomy defect may have had some effect on the amount of calcification, either by the addition of calcium compounds as such or by early assimilation of the minerals in the formation of new bone. Specimens having a high calcium content showed microscopically

13 Neuhaus, C. Ueber den Stoffwechsel des Granulationsgewebes (Atmung und Glykolyse), Beitr. z. path. Anat. u. z. allg. Path. **83**: 383-430, 1929.

the best developed bone, with formation of well defined spicules Leriche and Jung,¹⁴ in studying local utilization of calcium at sites of fracture, found a similar variability and generally a similar degree of calcification of the early callus. They ascribed the variations to varying degrees of decalcification of the fragments and of utilization of the mineral elements in laying down new bone. This effect was probably less in our work, since a rather large defect existed because of the osteotomy. Their results were obtained with callus from reduced human fractures.

The phosphatase activity started at a relatively low value, rising with active proliferation of bone. Because of the necessity of using soft tissue preparations this could not be followed far, but, as has been shown by other workers, the concentration may be expected to fall during restoration of the medullary cavity. In spite of the variability



Phosphatase activity in early callus

shown in the values for the different quantities studied, there was close correlation between the amount of calcification and the phosphatase activity. Fractures showing extensive calcium deposition in the callus with good roentgen evidence of early union and microscopic evidence of new bone formation all showed high levels of phosphatase activity. In combination with the lack of correlation between the other quantities this is strong evidence that the rapidity of healing of the fracture is dependent on the amount of phosphatase produced locally. In this study, the degree of healing in the early stages was not dependent so much on the age of the fracture as on the amount of phosphatase that has been produced. This was particularly well illustrated in the case of the second rabbit killed on the seventh day. The phosphatase activity

14 Leriche, R, and Jung, A. Documents concernant l'utilisation locale du calcium provenant d'un foyer d'osteolyse, etude sur les mecanismes de l'osteogenese. *Rev de chir*, Paris **76** 378-381, 1938.

was about one-tenth that observed in the first rabbit studied on the same day. The amount of calcification was also greatly less. Grossly and microscopically the region showed evidence of infection. This suggests that infected fractures show delayed healing, in part due to decreased phosphatase activity.

There was no definite shift in the values for blood phosphatase. As many values were below the initial level as were above it, and the mean showed no significant change. This is in agreement with the work of other investigators, who have found that there is no definite relation between the level of blood phosphatase and the healing of fractures.

SUMMARY

The relation of blood phosphatase, tissue phosphatase, tissue calcium and tissue metabolism was studied in a series of rabbits subjected to osteotomy.

There was an initial rise in tissue metabolism of the callus followed by a fall. There was an irregular increase in phosphatase activity and calcium deposition with time. The changes in concentration of serum phosphatase were not characteristic.

A close relation was found between the phosphatase activity of the callus and the amount of calcium deposition.

PHOSPHATASE ACTIVITY OF INFECTED FRACTURES

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AND

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OMAHA

In the course of an earlier investigation ¹ it was noted that a healing infected fracture showed a much lower level of phosphatase activity than did a sterile one of the same age. This suggested that retarded or suspended healing of infected fractures may be the result of diminished phosphatase activity. The literature concerning the relation between fractures and phosphatase activity in blood and bone has been reviewed previously ¹. It has been pointed out by Roe and Whitmore ² in a clinical study of phosphatase activity in chronic infections of bone that there was no uniform rise in the phosphatase content of the blood.

METHOD

Bilateral osteotomy with block resection of 1 cm of the shaft was done on the radiuses of adult rabbits, and at the same time blood was removed from the heart for initial determinations of the level of phosphatase. The osteotomy wound on one side was closed by a sterile technic. The osseous defect produced on the other side was infected by injecting into it 0.1 cc of a broth suspension of hemolytic streptococci. With the first animal of the series it was found that, although during the first week an inflammatory change was maintained, at the end of two or three weeks the infected side showed good healing and was indistinguishable from the sterile side. This series (3 rabbits), in which there was rapid healing of the fractures, has been designated series A. In order to maintain infection for a longer time a special technic was employed. The broth suspension of the organism was placed in a small gelatin capsule, which was sealed with collodion, the capsule

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1 Tollman, J P, Drummond, D H, McIntyre, A R, and Bisgard, J D. Tissue Metabolism and Phosphatase Activity in Early Callus, Arch Surg, this issue, p 43

2 Roe, J H, and Whitmore, R. Clinicopathologic Application of Serum Phosphatase Determination with Special Reference to Lesions of the Bones, Am J Clin Path 8 233-254, 1938

was then placed in the space between the bone fragments at the site of the osteotomy. This had the effect of sharply localizing the infection, allowing slow diffusion of the infected material into the tissues as the capsule disintegrated and adding a foreign body to help in keeping up the inflammatory change. By this method active infection was maintained for three weeks, after which the infected side showed healing to a degree only slightly inferior to that shown by the sterile side. This series of animals, with slowly healing fractures, has been designated as series B. At progressive intervals of one week postoperatively a rabbit was killed, blood was taken for determination of the level of serum phosphatase and the callus was dissected out from either side. After a small fragment had been removed for microscopic examination, each callus was weighed, macerated with 5 cc of 0.85 per cent solution of sodium chloride and allowed to stand in the ice box for twenty-four hours to extract the phosphatase. One cubic centimeter of the supernatant fluid was used for determination of the phosphatase content by the method of King and Armstrong.³ Determination of the value for serum phosphatase was made at the same time. The residual saline solution together with the fragments of tissue was evaporated to dryness at 110 C to obtain the dry weight of the specimen. The organic matter of the residue was decomposed by evaporation with nitric acid and ignition at red heat. The inorganic matter was taken up in nitric acid and was transferred to a centrifuge tube for determination of the calcium content by the method of Clark and Collip.⁴

RESULTS

The results of this work are summarized in tables 1 and 2. Both the dry and the wet weight of the tissue have been used in calculating the results. The dry weight was determined, since it has usually been considered as the primary standard of weight, but we feel that the wet weight is more significant here. Since the early callus is soft, edematous granulation tissue which is rather bulky, the wet weight more truly approximates the weight of active tissue present. Calculations based on the dry weight of such loose edematous tissue give rise to abnormally high values for phosphatase and calcium.

The first part of table 1 shows the changes in rabbits with rapidly healing infections. It is seen that the initial level of phosphatase was much lower in the infected side, and there was, similarly, a much smaller amount of calcium. For the sterile side there was a higher value for phosphatase and an increased amount of calcium. As the infected side began to heal and overcome the infection, it approached closely the characteristics of the sterile side. In fractures two and three weeks of age it was difficult to distinguish grossly or microscopically between the infected and the sterile side. This similarity in appearance was associated with almost identical values for calcium and phosphatase.

3 King, E. J., and Armstrong, A. R. A Convenient Method for Determining Serum and Bile Phosphatase Activity, *Canad. M. A. J.* **31**: 376, 1934.

4 Clark, E. P., and Collip, J. B. Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, *J. Biol. Chem.* **63**: 461-464, 1925.

Nevertheless, the mean values for the 3 rabbits of this series showed a difference in the levels of phosphatase and calcium between the infected and the noninfected side

TABLE 1—*Phosphatase Activity of Infected Fractures*

Age of Fracture, Days		Weight of Callus, Mg		Phosphatase in Callus, Units/Gm		Calcium in Callus, Mg /Gm		Blood Phosphatase	
		Wet	Dry	Wet	Dry	Wet	Dry	Initial	Final
Series A									
7	Sterile	89	28	1,200	3,800	9.4	30		
	Infected	65	14	246	1,140	0.5	2.1	11.6	14.7
14	Sterile	59	31	2,000	3,800	108	204		
	Infected	58	30	2,300	4,400	78	150	5.6	9.3
21	Sterile	55	35	1,300	2,100	126	200		
	Infected	30	19	1,300	2,000	87	137	2.5	3.8
Series B									
7	Sterile	37	8	1,500	7,100	28	130		
	Infected	45	19	220	530	5	11	7.3	9.2
14	Sterile	72	14	2,000	10,000	39	200		
	Infected	82	11	230	170	6.8	51	6.1	11.0
21	Sterile	68	37	1,800	3,400	62	300		
	Infected	106	48	400	1,000	10	23	3.5	7.6
28	Sterile	50	31	1,500	2,400	102	165		
	Infected	110	54	1,200	2,300	23	47	5.8	9.7
35	Sterile	54	35	2,300	3,500	58	90		
	Infected	52	20	500	1,400	8.1	13	4.7	6.0
Mean Values for Calcium and Phosphatase									
		Calcium in Wet Callus, Mg /Gm				Phosphatase in Wet Callus, Unit/Gm			
Series A									
Sterile		81				1,500			
Infected		55				1,300			
Series B									
Sterile		58				1,800			
Infected		11				510			

TABLE 2—*Changes in Blood Phosphatase*

	Initial	Final
Series A		
7 days	11.6	14.7
14 days	5.6	9.3
21 days	2.5	3.8
Mean	6.6	9.3
Series B		
7 days	7.3	9.2
14 days	6.1	11.0
21 days	3.5	7.6
28 days	5.8	9.7
35 days	4.7	6.0
Mean	5.5	8.7

In series B the effect of sustained infection was apparent. The infected side showed a more marked difference from the sterile one and the difference was maintained longer. It was not until the fourth and fifth week that the gross and microscopic appearance and the phosphatase

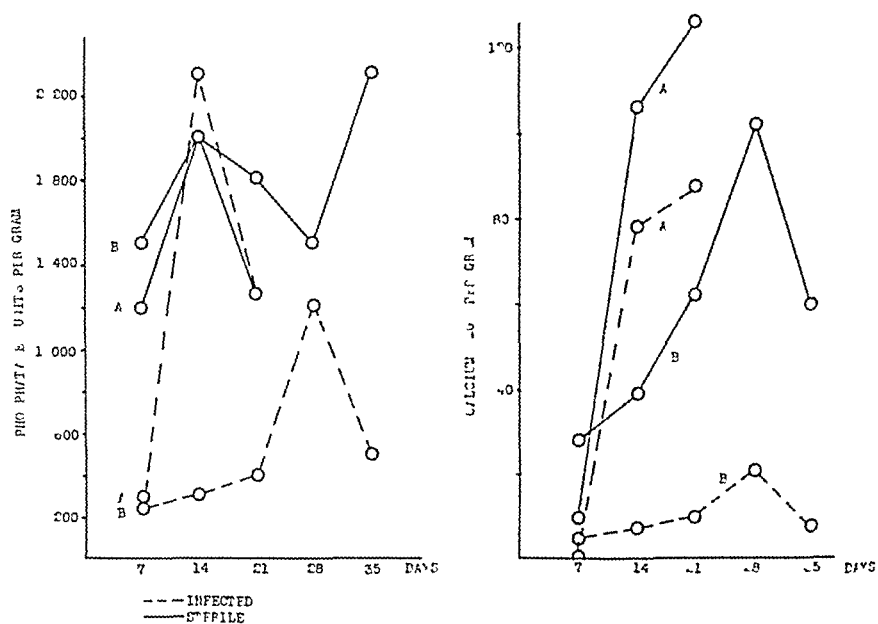


Chart 1—Values for phosphatase and calcium in the infected and in the sterile callus

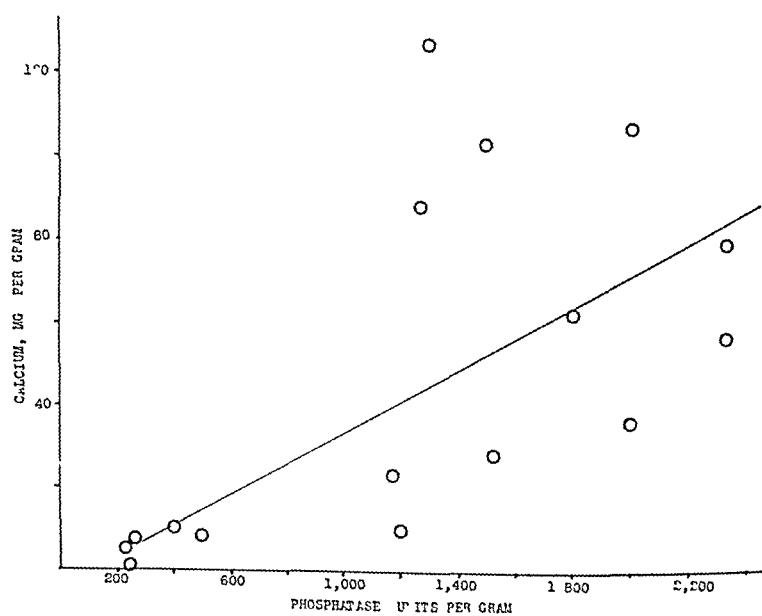


Chart 2—Relation between the phosphatase activity and the degree of calcification

and calcium concentration on the infected side began to resemble those on the uninfected one. This tendency for the phosphatase and calcium content of the infected callus to approach that of the sterile callus is clearly illustrated in chart 1. Chart 2 shows the relation between the phosphatase activity and the degree of calcification. This correlation is not as close as was shown previously by some of us.¹

It will be observed that the values for blood phosphatase increased over the initial levels during the healing of the infected fractures (table 2). The consensus is that there is no characteristic change in the level of phosphatase in cases of fracture due to osteomyelitis. In our previous work¹ with sterile fractures in rabbits there was no consistent change in the values for blood phosphatase. In infected fractures there was a uniform rise above the initial values, but, since normal limits were not exceeded, determinations of the values for phosphatase in the blood would have no clinical value.

SUMMARY

In this study, the levels of phosphatase and of calcium in infected fractures in rabbits were lower than in sterile fractures.

There was a uniform rise in the level of blood phosphatase in the infected series.

In both infected and sterile fractures, high levels of phosphatase activity were associated with the presence of large calcium deposits.

THE CARPUS, WITH REFERENCE TO THE FRACTURED NAVICULAR BONE

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When a certain fracture frequently does not respond to the forms of treatment which usually produce satisfactory results in other fractures, there is, as a rule, much speculation as to the causes of failure of healing, and many suggestions are advanced for the proper form of treatment to be employed

Injuries to the carpal bones, with one or two exceptions practically always heal when they are reduced properly and immobilized for a short time. The frequent exception to this rule is fracture of the carpal navicular bone. Aseptic necrosis of the lunate bone not uncommonly gives an unsatisfactory result, but dislocations and the other fractures, if promptly reduced and immobilized, are generally followed by good return of function and usefulness of the hand. Although fractures and dislocations of the carpus are not common (approximately 2 per cent of all fractures, according to a review of 4,500 fractures at the Massachusetts General Hospital), they are extremely important injuries, because failure to make a careful diagnosis of the injury, based on a thorough knowledge of the anatomy of the part, frequently results in delayed or misguided treatment, and a disabled hand may be the ultimate result.

DEVELOPMENT OF THE CARPUS

The development of the carpal bones usually follows a definite plan, and anatomic variations are infrequent. The bones are cartilaginous at birth, and during the first year the ossification centers of only the capitate and hamate bones appear. The remaining ones appear between the second and the eighth year (fig 1), except the pisiform bone, which does not appear until the tenth year or later (fig 2). Inflammatory processes may cause the ossification centers to appear earlier than normal (fig 3). Tuberculosis was the exciting cause in the case illustrated. Poliomyelitis or prolonged congestion of the extremity from any cause may have the same effect. Delayed development of the carpus may occur in chondrodystrophies and as a familial characteristic, as recorded by Hess and Abramson,¹ usually these bones develop from a single ossification center, but there are exceptions. The most common of the

From the Fracture Clinic of the Massachusetts General Hospital

1 Hess, A. F., and Abramson, H. J. *Pediat* 3 158, 1933

anatomic variations is the bipartite navicular bone. I have seen no such anomaly, and I wonder, as do others (Wette²), whether such an appearance may not always be due to an old unrecognized fracture which has produced a pseudarthrosis. Careful investigators (Dwight,³ Todd,⁴ Pfitzner,⁵ Speed⁶ and others), however, have reported such variations and have stated that they may also occur in the capitate bone. Usually

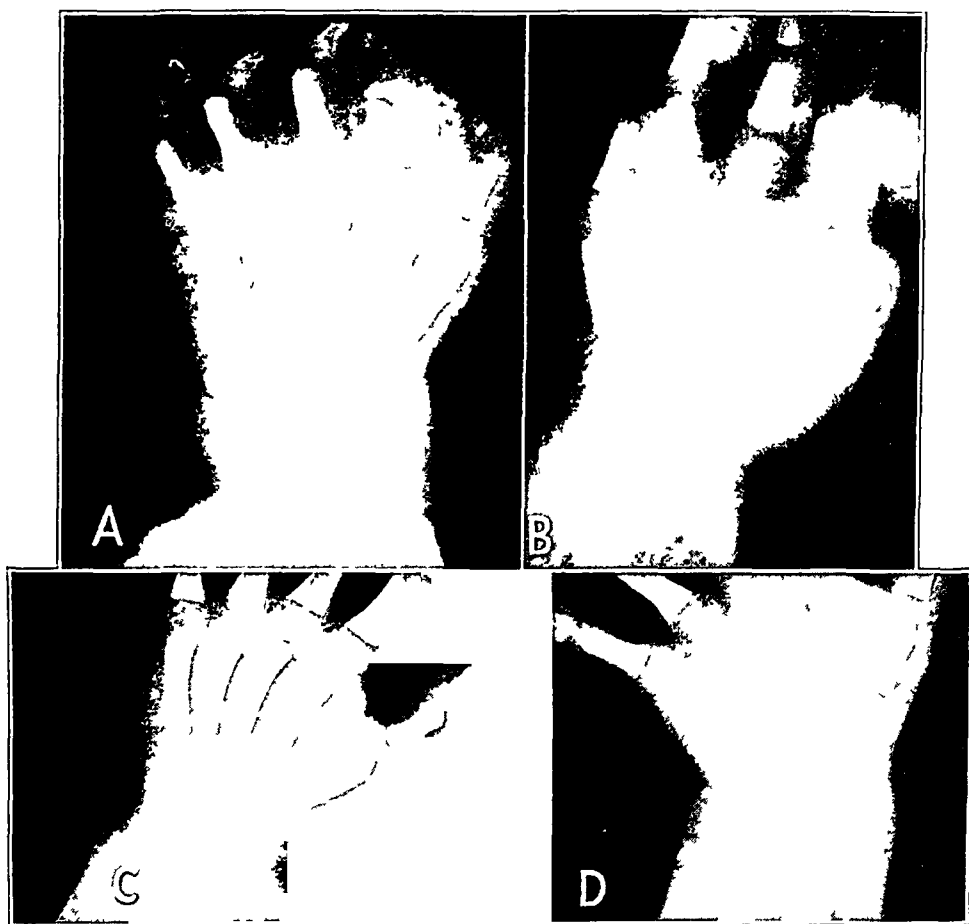


Fig 1—Early stages in the development of the carpus. In *A*, at birth, the carpus is entirely cartilaginous, in *B*, at 6 months, the ossification centers of the hamate and capitate bones are present, *C*, at one year, in *D*, at 2 years, the ossification centers of the hamate, capitate and triangular bones are present

2 Wette, W. *Arch f orthop u Unfall-Chir* 29 320, 1931

3 Dwight, T. *Variations of the Bones of the Hands and Feet*, Philadelphia, J B Lippincott Company, 1907

4 Todd, A H. *Brit J Surg* 9 7, 1921

5 Pfitzner, W. *Ztschr f Morphol u Anthropol* 2 77, 1900

6 Speed, K. *Traumatic Injuries to the Carpus*, New York, D Appleton and Company, 1925

these anatomic variations are bilateral, and there may be no history of injury Todd⁴ stated that they may be associated with other congenital abnormalities, such as web fingers and premature synostosis of the phalanges In the bipartite navicular bone, he wrote, "the line of division runs obliquely from near the outer end of the articular surface for the radius to about the middle of the concavity for the head of the os magnum"³—in other words directly through the "waist" of the bone

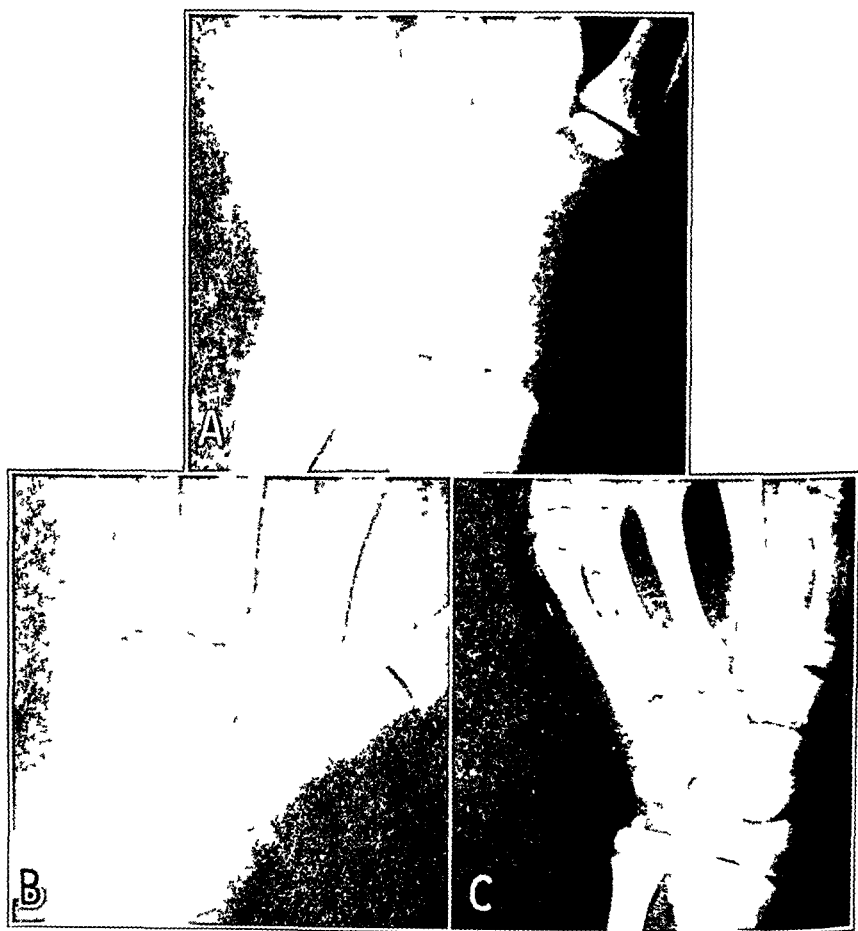


Fig 2—Later stages in the development of the carpus In *A*, at 6 years, the capitate, hamate, triangular and lunate bones are present while the centers of the navicular and the multangular bones are just appearing, in *B*, at 7 years, all the bones are present but the pisiform bone, in *C*, at 12 years, all the bones are ossified

Examining 1,456 wrists, Pfitzner⁵ found in 9 complete bipartite navicular bones, in 29, the bone was partially cleft Codman and Chase⁶ however, found no bipartite navicular bones in 1,040 wrists examined No instances of failure of appearance of any carpal bone have been reported, and no accessory bones have been recorded

⁷ Codman, E A, and Chase, H M Ann Surg 41 321 and 863, 1905

BLOOD SUPPLY OF THE CARPUS

The blood supply to the carpus is relatively inadequate. There are small nutrient arteries, which derive their blood supply from terminal twigs of the ulnar and radial arteries and which, after being carried

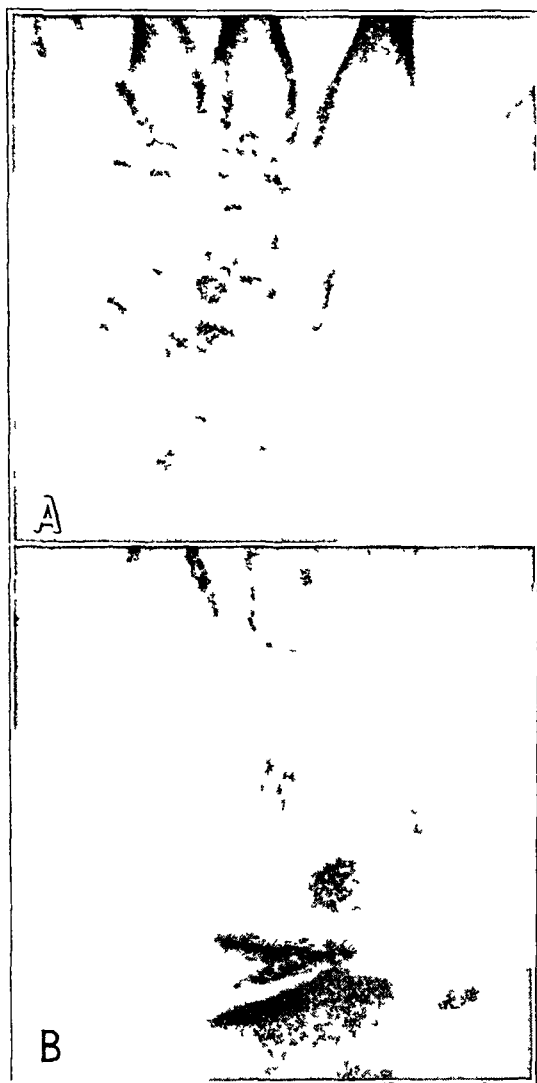


Fig 3—The effect of inflammation on the development of the carpus, shown by roentgenograms of both hands of a 6 year old child. In *A* the diseased hand, all the bones are well calcified, in *B*, the normal hand, only the ossification centers of the capitate and the hamate bone are fully developed.

along supporting ligaments, enter the fibrous covering representing the periosteum. Lexer's⁸ preparations showing the circulation of the navicu-

8 Lexer, cited by Kuchel, W. Munchen med Wchnschr 80 1350, 1933

lari bone demonstrated two nutrient vessels, one entering the tuberosity and another, a larger one, entering the middle of the body of the bone and giving off proximal and distal branches (fig 4) Johnson⁹ studied the blood supply of the navicular bone in dogs in relation to repair of bones and concluded that the supply was adequate

ANATOMY

The importance of the anatomic arrangement of the carpal bones cannot be too strongly emphasized (fig 5) to one who expects to treat

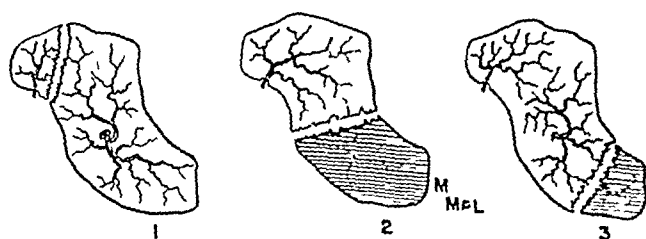


Fig 4—Blood supply to the navicular bone (after Lexer)

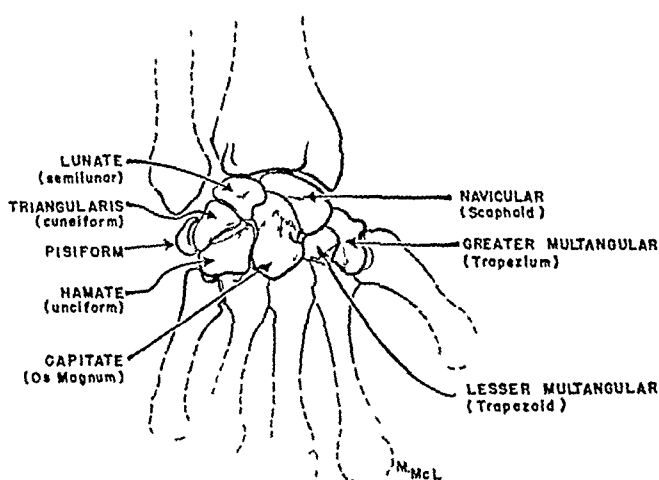


Fig 5—Anatomic arrangement of the carpal bones

these carpal injuries. Indistinct fractures and minor subluxations are frequently overlooked, not through failure to take roentgenograms but through ignorance of the anatomy of the parts in various positions of the hand. Such negligence had occurred in the following case (fig 6)

CASE 1—J L, a man aged 22, was admitted to the hospital on May 11, 1934. Three months before, he had fallen, striking the right wrist, he had been seen at

9 Johnson, R W, Jr. J Bone & Joint Surg 9 482, 1927

another hospital, where roentgenograms were pronounced normal. Two weeks before admission, the hand had been forced into dorsiflexion, increasing pain in the wrist. Roentgenograms revealed fracture of the navicular bone in the midportion. The patient was given a leather wristlet, which he wore four months. Roentgenograms at the end of that time showed bony union.

End Result—Examination after two years showed the patient free of symptoms and his motions normal. Roentgenograms showed bony union.

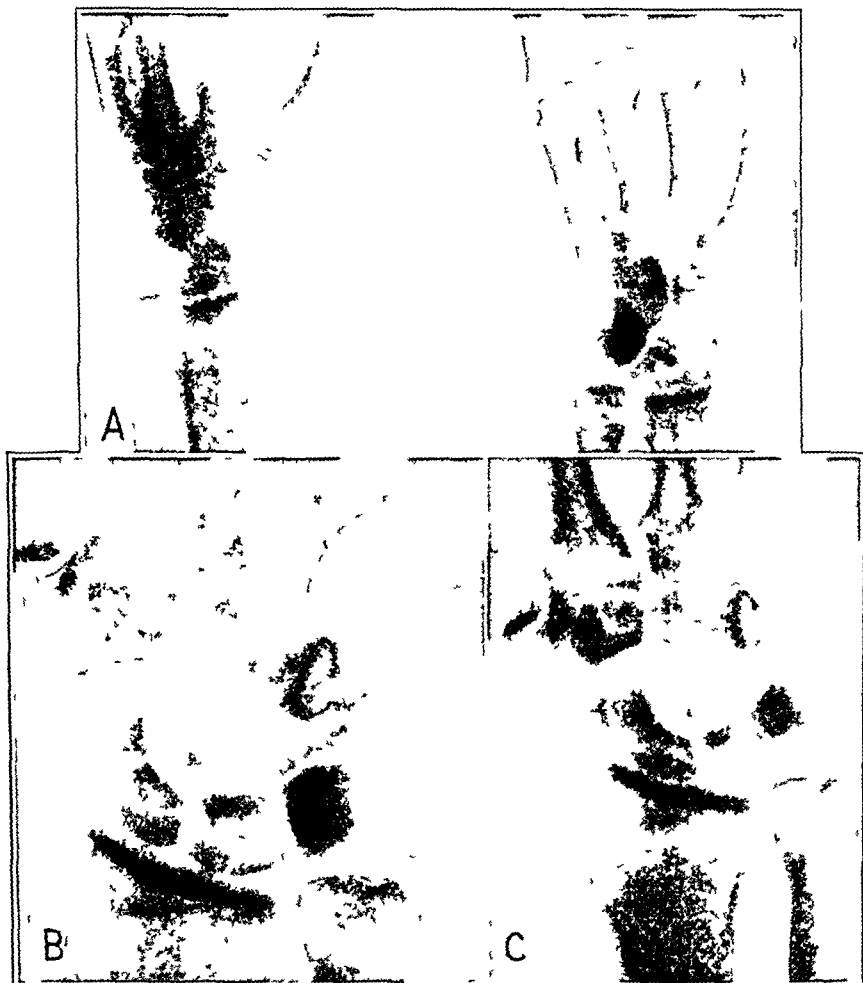


Fig 6 (case 1)—Roentgenograms of a navicular fracture. *A*, anteroposterior and oblique views made at the time of the inquiry, showing a faint line across the waist of the navicular bone, undoubtedly representing the original fracture, although the injury was not discovered in the original examination of the roentgenograms, *B*, three months later, showing a well developed fracture line, *C*, after the wearing of a leather wristlet for ten months, showing the fracture well healed.

Although the anatomy of these carpal bones is too well described in the usual textbooks to necessitate discussion here, certain facts may be emphasized. The first row of the carpus, consisting of the navicular,

lunate, triangular and pisiform bones, is on its surfaces largely cartilaginous, the remaining portions serve for ligamentous attachments. The second row, made up of the greater and lesser multangular, the capitate and the hamate bone, is less cartilaginous but is more extensively covered by the ligamentous attachments. This row is more firmly held together by the supporting ligaments than are the navicular and the lunate bone, which are more exposed to trauma because of their location and their movable articulations with the radius. On the volar surface there are tendinous attachments only to the pisiform, hamate and greater multangular bones, while on the dorsal surface there are none. The navicular bone, which is of most concern in this discussion, articulates from the dorsum with the radius, the greater and the lesser multangular bone and the lunate bone. On its volar surface the navicular bone is in contact with the greater and the lesser multangular bone, the capitate bone, the lunate bone and the radius.

PATHOLOGY

When any bone is fractured, the blood supply to the fragments is temporarily interrupted. This is particularly true of the carpal bones, and especially so of the carpal navicular bone. If the fracture line runs directly through the bifurcation of the main artery, which enters the midportion of the navicular bone, nutrition to the proximal fragment is interrupted, the distal fragment is nourished, however, by the artery entering the tubercle (fig 4). Such interference with the blood supply to the proximal fragment explains the failure of union in a large percentage of navicular fractures in the middle and proximal regions. After immediate reduction and fixation are carried out, there is rather quick restoration of blood vessels across the fracture line. If treatment is delayed, a scar forms and the blood channels are sealed off. Even after several weeks has elapsed, it is possible to promote restoration of blood supply to the fragments if immobilization is carried out for a sufficient length of time, as illustrated in case 1. If nonunion does become established, if one or both fragments show in a roentgenogram a density greater than that of the other carpal bones, it is probable that pseudarthrosis is permanent and that no amount of fixation will promote formation of new blood vessels (fig 7). In prolonged nonunion, vacuolation may result and only a shell of the navicular bone remain (case 13, fig 17), the fragments taking on much the same appearance as those of the lunate bone in Kienbock's disease.

Johnson⁹ in his experiments on dogs found that the fragments of the fractured navicular bone were not to any extent deprived of their blood supply. He expressed the opinion that the reparative process is carried out by cancellous bone but is slower in the navicular bone than

in the long bones and that the absence of periosteal callus is an important factor in the slow union of the navicular bone. He discounted the importance of the lytic action of the synovial fluid, a function which was advocated by Murray¹⁰ as a factor in producing nonunion. Johnson⁹ stated also that undue mobility at the fracture site is not a factor in producing delayed union, since the fragments are so closely apposed. Delayed union, therefore, is probably produced by no one factor but is brought about by a combination of excess motion, interference with blood supply, possibly the presence of synovial fluid and the absence of periosteal callus.



Fig 7—Nonunion of the fractured navicular bone, complete and permanent. Possibly a bone graft and drilling may produce union, but external fixation never will.

DIAGNOSIS BY ROENTGEN EXAMINATION

The hand may be placed in various positions so that in the roentgenogram the bones may appear to have an abnormal relationship (fig 8). If the anteroposterior view of the navicular bone is made with the wrist in radial deviation the bone may appear shortened or subluxated, whereas with the wrist in ulnar deviation the true long axis of the bone is visible and any abnormality is more easily seen. It is therefore not only important to have standardized methods of roentgen technic but also necessary to have adequate knowledge of the relationships of the carpus in the various positions of the hands. For studying

¹⁰ Murray, C. R. *Ann Surg* 93:961, 1931.

the navicular bone, both hands should be photographed on the same plate (fig 9), the anteroposterior view with the hands in ulnar deviation and the oblique views with the hands in midpronation are most important

MECHANISM, DIAGNOSIS AND TYPES OF INJURY

Fracture of the navicular bone is by far the most common injury to the carpal bones. In our series of 110 carpal injuries it occurred sixty-eight times, either alone or in conjunction with other injuries to the wrist. (The accompanying table shows the types of injuries to the carpal bones.) Patients are usually of the male sex, especially young adults who are exposed to severe trauma. In most instances the injury occurs in acute dorsiflexion of the wrist, force being applied indirectly



Fig 8—Apparent, not actual, fracture of the navicular bone. Roentgenograms of the hand. *A*, in radial deviation, showing an apparent fracture of the navicular bone, *B*, in ulnar deviation, showing long axis of the bone and revealing no fracture.

Types of Injuries of the Carpal Bones

	No. of Cases
Fractured navicular bone, recent, without other carpal injury	34
Fractured navicular bone, old, without other carpal injury	26
Fractured navicular bone with other carpal injury	8
Dislocated lunate bone without other carpal injury	8
Dislocated lunate bone with other carpal injury	3
Retrolunar dislocation of capitate bone	6
Fractured lunate bone	5
Kienbock's disease	6
Miscellaneous fractures including chip fractures	11
Cyst of lunate bone	1
Cyst of navicular bone	1
Congenital fusion of triangular and lunate bones	1

to the navicular bone through the second and first metacarpal bones and the second row of the carpus, or the blow may be received directly on the tubercle of the bone. In 2 cases in the series the navicular bone was fractured by a fall which forced the hand sharply into radial deviation and palmar flexion. Given a patient with such a history, with pain in the wrist, which is moderately swollen but without deformity, with tenderness over the "snuff-box" or over the tubercle of the navicular bone, one must strongly suspect injury to this bone. Motions may be only moderately limited, and the usual signs of fracture of a long bone are absent. Roentgenograms taken carefully with the hand in special positions are necessary. Usually the fracture occurs in one of three

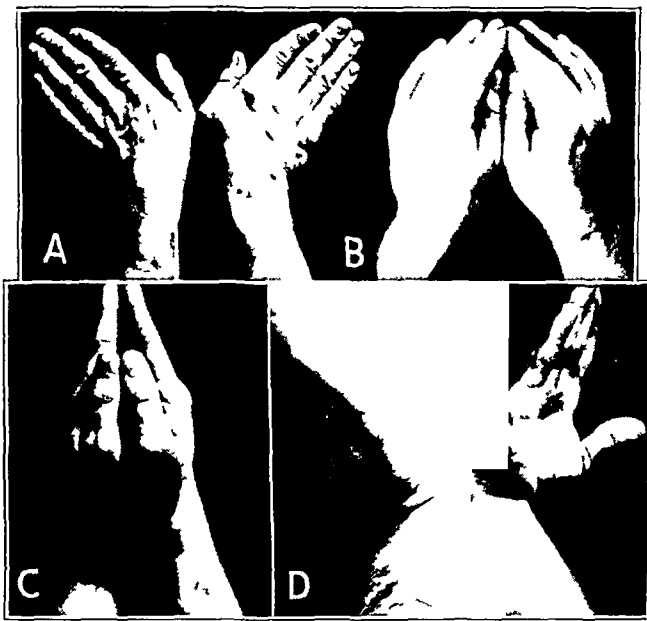


Fig 9—Positions of hands for roentgenograms of navicular bone. *A*, ulnar deviation, *B*, midpronation, oblique view, *C*, lateral, *D*, extreme pronation, oblique view.

places (fig 10), listed here in order of frequency: the central portion, or "waist," of the bone (type 1), the junction of the proximal and the middle third (type 2), and the tubercle of the bone (type 3). To produce fractures of types 1 and 2, the wrist must be forced sharply into dorsiflexion or palmar flexion, with sharp radial deviation. Such a position compresses the navicular bone between the greater multangular bone, the radius and the lunate bone. A fracture of type 3 is sustained when the hand is forced into dorsiflexion and ulnar deviation. In this position the tuberosity is pulled off by its ligamentous attachments. Rarely is the navicular bone fractured by a direct blow; when it is, the

fracture may be comminuted, of type 4 (fig 11). Occasionally the fracture, although present, may not be demonstrable because of the impaction (case 1). In such a case, if the clinical findings are consistent with a diagnosis of navicular fracture the wrist should be immobilized at once, and further roentgenograms should be made three weeks and possibly six weeks afterward, when the fracture will be demonstrable because of the absorption that always takes place at the fracture line.

TREATMENT OF NAVICULAR FRACTURES

For all fresh fractures of the carpal navicular bone (type 1), for fractures through the midportion (type 2) and for fractures at the

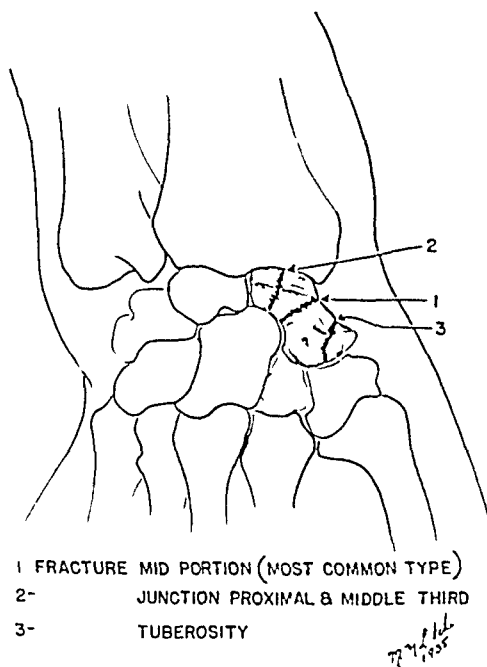


Fig 10—Sites of fracture in the navicular bone

junction of the proximal and the middle third, whether partial or complete, with or without separation of the fragments, early and complete immobilization of the thumb, hand and lower two thirds of the forearm should be carried out (fig 12). It is ideal to immobilize the thumb completely, the wrist should be in a position of approximately 30 degrees dorsiflexion and 15 degrees radial deviation, since this position approximates the fractured surfaces. The fingers are left free and motion of them is encouraged from the start. Bohler¹¹ and his colleagues,

11 Bohler, L. *Wien med Wchnschr* 85 803, 1935, *The Treatment of Fractures*, ed 4, translated by E. W. H. Groves, Baltimore, William Wood & Company, 1935.

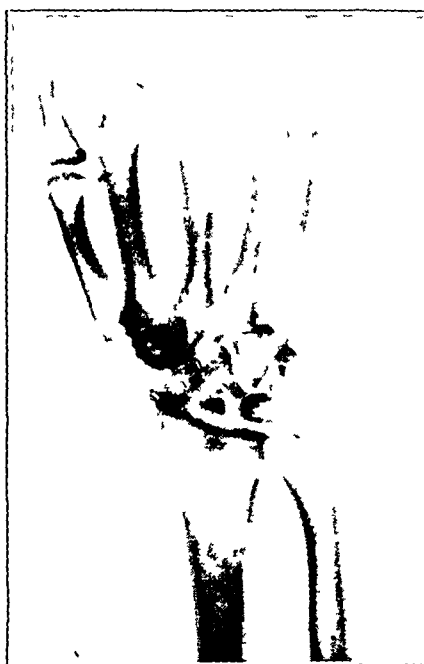


Fig 11—Comminuted fracture of the carpal navicular bone. This type of fracture is best treated by primary excision of all fragments. Reduction cannot be effected, and if operation is not done early traumatic arthritis is certain to follow.

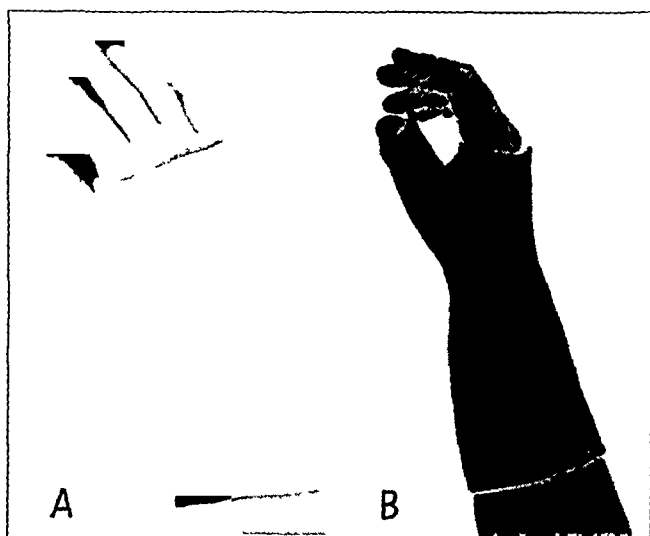


Fig 12—Circular plaster splint for immobilization of fractured navicular bone. *A*, anteroposterior view, *B*, lateral view.

Schneck¹² and Watson-Jones¹³ have advocated use of the light, non-padded dorsal splint. I have felt that the circular plaster offers better fixation and is less apt to be disturbed by the use of the hand. The plaster should be worn until union is demonstrable in roentgenograms. Rarely is this union accomplished in less than eight weeks. When union is established it is well to supply the patient with a leather wristlet made from a plaster model, which holds the hand in a position of slight dorsiflexion. It can be worn when the patient is at work and discarded at night. I see no value in physical therapy in this type of fracture. In many of my own cases, I feel sure, it has been harmful, for too much reliance has been placed on increasing the blood supply by heat and massage, and not enough attention has been paid to prolonged immobilization. If necessary, immobilization should be carried out for four months before one admits that the patient has nonunion. If at the end of that time nonunion seems to be definitely established (the diagnosis of this is based entirely on roentgenograms), operative treatment is indicated. Of 34 patients with recent navicular fractures, 12 who were examined at the end of one year or longer had no disability. Yearly end results were not obtained for the remaining 22 patients. Böhler,¹¹ after experience with 300 recent navicular fractures, stated that all such fractures heal if immobilization is carried out for six weeks. Schneck¹² in his excellent monograph agreed essentially with this point of view. He reported union in 100 per cent of his cases in which the fractures were no more than three weeks old when treatment was started. Haldeman and Soto-Hall¹⁴ secured union by plaster fixation in 75 per cent of 16 recent navicular fractures. Hirsch¹⁵ stated that all fresh navicular fractures unite by bone if they are immobilized for as long as six weeks. Wette² recommended immobilization for eight weeks or longer. Speed¹⁶ advocated prolonged immobilization.

Fractures of the tubercle of the navicular bone (type 3) always heal, for a fracture of this kind is largely extra-articular and the blood supply to both fragments is maintained. A fracture of type 4, or the comminuted fracture of the navicular bone, is in all probability best treated by primary excision of the entire navicular bone. To leave the comminuted and displaced fragments to create abnormal friction against the surrounding carpal bones and the radius leads to traumatic arthritis, which is permanent if operation is delayed.

12 Schneck, F. *Ergebn d Chir u Orthop* **23** 1, 1930, *Zentralbl f Chir* **57** 2600, 1930.

13 Watson-Jones, R. *Brit J Surg* **22** 63, 1934.

14 Haldeman, K. O., and Soto-Hall, R. *J Bone & Joint Surg* **16** 822, 1934.

15 Hirsch, M. *Wien med Wchnschr* **85** 803, 1935.

16 Speed, K. *J Bone & Joint Surg* **17** 965, 1935. *Surg, Gynec & Obst* **64** 9, 1937.

OPERATIVE TREATMENT FOR NONUNION OF THE CARPAL
NAVICULAR BONE

Excision of One Fragment—Prior to ten years ago, the accepted form of therapy for nonunion of the carpal navicular bone in most clinics was excision of one fragment of the navicular bone. The end results of such operations left much to be desired.

Excision of the Entire Navicular Bone—Certain surgeons have advocated the removal of the entire bone as treatment for nonunion. Hirsch¹⁵ reported excellent results in 9 cases following operative removal, with perfect return of function of the wrist and no trace of radial deviation. He advocated early extirpation of the bone before traumatic arthritis in surrounding bones develops. He emphasized the absolute necessity of careful removal of every fragment of the bone and the articular cartilage without damage to the surrounding bones. Operative removal of the entire navicular bone, he said, produces just as good results as does external fixation and in much less time, an excellent return of function may be expected in six weeks. Gurd,¹⁷ of Montreal, is another advocate of excision of the carpal navicular bone for delayed union or for nonunion, he expressed the opinion that it might be an accepted method for primary treatment of navicular fractures. He stated that he had never had cause to regret the removal of either the navicular or the lunate bone, and had been better pleased with the results of this form of operation than with those following either conservative treatment or the use of a bone graft. He would emphasize, he said, the fact that the operation is not easy and that it should be undertaken only by a careful surgeon who knows thoroughly the anatomy of this region. Bohler,¹¹ on the other hand, stated

I have never seen a case in which the usefulness of the hand has returned to normal after removal of the navicular bone. Kemper has collected 60 cases of removal of the navicular and lunate bones, in all of these function of the hand was poor. In cases operated on early the mobility of the wrist may remain good, but the strength of the hand is always weakened.

The only case in our series in which the fracture was treated by excision is reported here (fig 13).

CASE 2—E. deB., a man aged 20, was admitted to the hospital in May 1937. Six months previously he had injured the right wrist while boxing. A splint applied to the wrist by the local physician was worn for one month. The wrist continued to be painful. Examination on admittance showed marked thickening of the wrist in anteroposterior diameter, limitation of flexion, extension, pronation, supination and deviation and tenderness to pressure over the region of the navicular bone. Roentgenograms revealed rotation and subluxation of the navicular bone.

17 Gurd, F. B. Personal communication to the author.

Operation—By a dorsoradial approach, the navicular bone was exposed and was found rotated so that the proximal radial articular surface was pointing to the dorsum. There was evidence of an old fracture of this surface, and there were traumatic changes on the articular surface of the radius. Slight posterior displacement of the capitate bone on the lunate bone was also visible. The navicular bone was excised in toto (fig 13 C and D). The wound was closed in layers. A light plaster splint was applied to hold the wrist in slight dorsiflexion and ulnar deviation for three weeks.

End Result—The patient went back to work, and resumed boxing six months after the operation. Two years after the operation he was reexamined, he con-

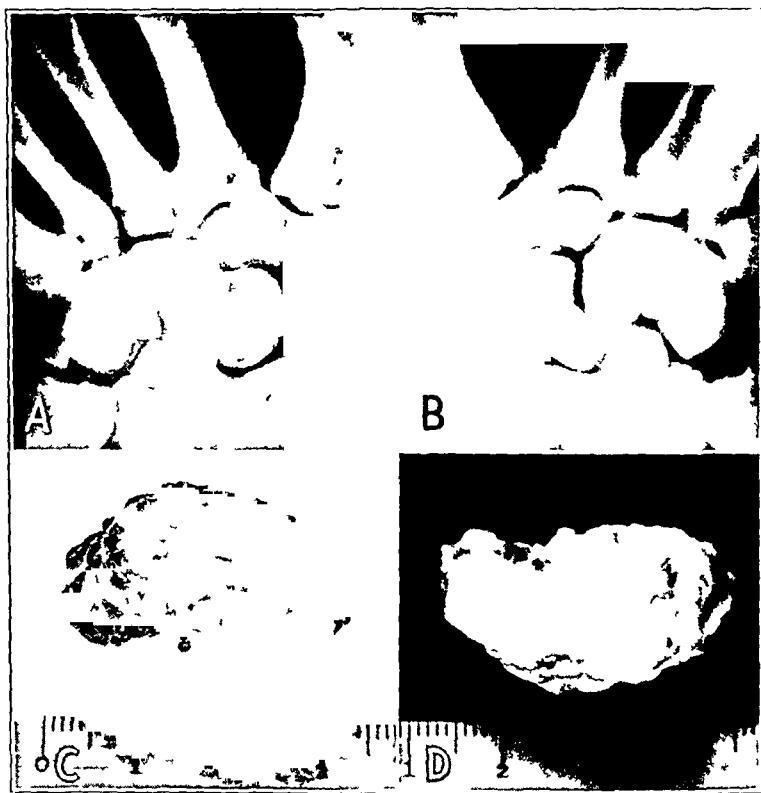


Fig 13 (case 2) —A, the fractured hand, shows the rotation of the navicular bone with depression on the articular surface of the radius, B, the opposite (normal) hand, C shows the radial articular surface of the navicular bone, which was subluxated, and the cartilaginous surface, which was compressed from the old injury, D, articular surface for capitate bone, showing no traumatic change.

fessed to some discomfort on the ulnar side of the hand during heavy work. Examination revealed thickening of the wrist. Articular motions were moderately restricted in palmar flexion and radial deviation but practically normal in ulnar deviation and dorsiflexion. The grip of the hand was slightly weakened.

The Method of Drilling—Another method of treatment of the ununited navicular bone has been that of drilling, a method which has

been advocated chiefly by Beck,¹⁸ Speed,¹⁶ Schneck¹² and Steindler.¹⁹ Speed¹⁶ recommended delaying the operation of drilling for six or eight months if adequate external fixation can be maintained during that time. The advocates of this method have suggested that in drilling one should approach the bone through the tabatiere and, using a $\frac{1}{8}$ inch (0.3 cm) drill, should make one or more drill holes across the fracture line into the proximal fragment. Speed¹⁶ said that he doubted the necessity of any graft and recommended following the drilling with plaster fixation of the wrist in dorsiflexion and radial deviation.

My experience with drilling has been confined to 3 cases—a case in which the fracture has united by bone, another in which there has been great improvement and there seems to be a strong fibrous union, and a third in which the treatment was a failure, because pain persists and there is marked limitation of motion.

The Autogenous Bone Graft—The other method of attack on delayed union or nonunion of the navicular bone is that of the autogenous bone graft. The first advocate of this procedure was Adams,²⁰ who in 1928 demonstrated a case in which bony union had been established by introducing a slot graft from the radius into the navicular bone. Others who have advocated this method are Murray,²¹ Burnett,²² Ethan H. Smith²³ and Allen.²⁴ This form of treatment has appealed more to my colleagues and me than the other forms described, and we have used it in the majority of the cases in which we have operated. If one considers the reasons for the frequent nonunion of the navicular bone, one must think in terms of blood supply and of the free motion through which the navicular bone normally travels as compared with the other carpal bones. Therefore, the combination of drilling and the introduction of a bone peg offers the best chance of reestablishing blood supply and at the same time of securing fixation of the fragments. In the early cases the graft was placed in a slot on the dorsum of the navicular bone across the fracture line. Recently it has been inserted through the drill hole from the distal to the proximal fragment. Objections to the slot graft are that it is necessary to expose too much of the dorsum of the bone and to interfere with the blood supply to this region, that too much bone is sacrificed from the navicular bone, and that fixation with

18 Beck, cited by Schneck¹²

19 Steindler, A. *Surg., Gynec. & Obst.* 58:487, 1934

20 Adams, J. D., and Leonard, R. D. *New England J. Med.* 198:401, 1928

21 Murray, W. G. *Brit. J. Surg.* 22:63, 1934; *Surg., Gynec. & Obst.* 60:540, 1935

22 Burnett, J. H. *Surg., Gynec. & Obst.* 60:529, 1935

23 Smith, E. H. *M. Rec.* 139:655, 1934

24 Allen, A. W. *Personal communication to the author*

the slot graft is not as secure as that with the dowel graft. The advantages of exposing the navicular bone over the dorsum are that the fractured surfaces of the bone can be freshened, that the fragments can be more closely approximated and that the exact position of the graft can be determined. In one of my cases in which the fracture was treated by introducing the graft through the drill hole, the proximal fragment was separated from the distal fragment by the graft and complete bony union was not established although the graft did unite with both fragments (case 15). The likelihood of such a result is a disadvantage of the method of introducing the bone graft through the drill hole.

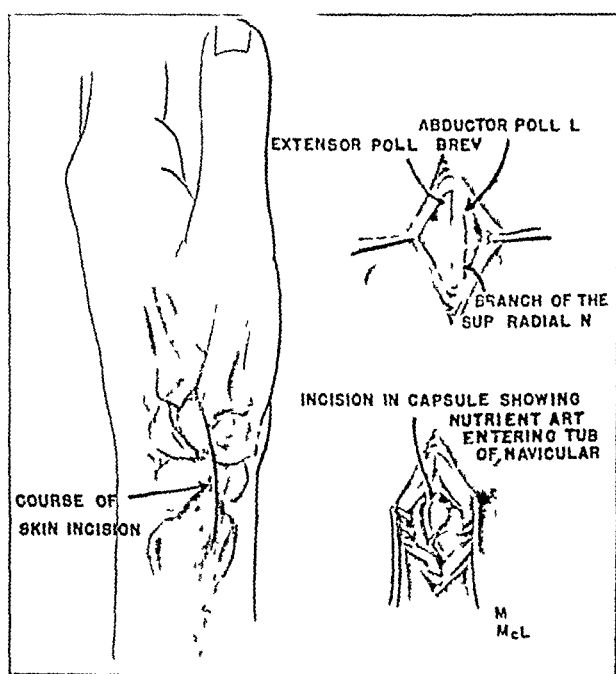


Fig 14—Radial approach to the navicular bone

Murray,²¹ of Toronto, advised exposing the navicular bone through a curved incision over the volar and radial aspects of the wrist (fig 14), nipping away with a rongeur a small portion of the tubercle of the bone, drilling a large hole through the bone from this point and introducing the graft. With this method Murray has secured bony union in a high percentage of cases. Burnett²² has also been partial to this method, and through it many of his patients have been rendered free of symptoms, though all the fractures have not united by bone.

At the Massachusetts General Hospital, in 16 cases of nonunion of the navicular bone treatment by the bone grafting operation was applied. End results can be given for only 13 of the cases, for 3, end results cannot be given because the operations were performed too recently. The

average duration of nonunion in these 16 cases was twenty-three months. The operative technic is as follows (fig 15). A 5 cm longitudinal incision is made over the dorsum of the wrist midway between the radial styloid process and the dorsal radial prominence. The abductor pollicis longus and the extensor pollicis brevis tendon lie to the radial side of the incision. The extensor carpi radialis longus, the extensor carpi radialis brevis and the abductor pollicis longus tendon are retracted to the ulnar side. The dorsal ligament of the wrist is incised in line with the incision in the skin. The radial articulating surface of the navicular bone comes into view. The ligamentous attachments to the groove of the dorsum of the navicular bone are gently reflected with

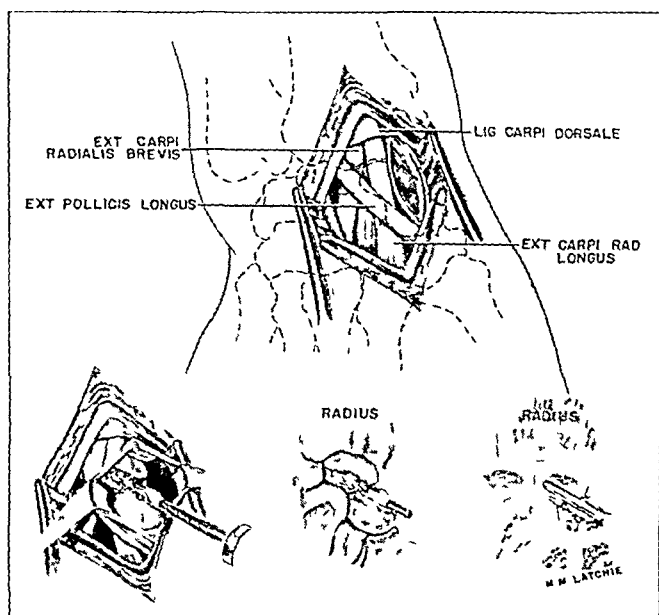


Fig 15—Dorsoradial approach to the navicular bone

sharp dissection until the fracture line is identified. The hand is then placed in ulnar deviation, and with a small spatula between the radius and the navicular bone the proximal fragment is held (fig 16). A $\frac{1}{8}$ inch drill hole is started well out on the distal fragment, as near the tubercle as possible, and continued across the fracture line well into the proximal fragment. The drill is kept about in line with the first metacarpal bone, and the wrist is held in ulnar deviation. When the graft has been removed from the crest of the tibia it is shaped to fit the drill hole and inserted across the fracture line into the proximal fragment. The protruding portion of the graft is nipped off with a rongeur and the dorsal ligament is carefully repaired with fine catgut or silk. The tendons are allowed to fall into place and the wound is

closed. A plaster casing similar to that previously described is then applied. In general, the period of convalescence is the same as that for fresh fractures of the navicular bone.

There follows a record of each case in which the autogenous bone graft operation has been performed.

REPORT OF CASES

CASE 3—R. M., a man aged 36, was admitted to the hospital on Feb. 29, 1928. He had fallen on a dorsiflexed hand one year before and had received no treatment. Roentgenograms showed nonunion of the navicular bone. Operation consisted in application of a slot graft from the radius to the navicular bone. The patient reported one year later that he began working five weeks after the operation,

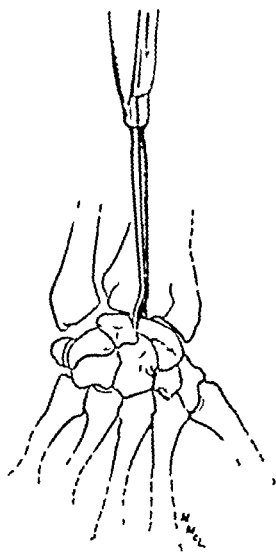


Fig. 16—Spatula used for holding proximal fragment of navicular bone.

there was no pain and his motions were good. Roentgenograms did not show complete bony union. Examined eight years after the operation, the patient was free of symptoms and was working as a railroad car inspector. Roentgenograms revealed irregularity of the fracture line but no change in the relationship of the fragments in various positions of the hand. There is probably bony union.

CASE 4—J. B., a man aged 20, was admitted to the hospital on Jan. 14, 1928. He had fallen on an outstretched hand one year and a half before, pain in the wrist had continued, and he had received no treatment. Roentgenograms showed nonunion of the navicular bone. The operation consisted of insertion of a slot graft from the radius. The patient returned to work in four months. Four years later there was slight limitation of motion in dorsiflexion and palmar flexion. Roentgenograms showed the fracture line, and there seemed to be strong fibrous union.

CASE 5—W. F., a man aged 21, was admitted to the hospital on March 7, 1929. Six months before, he had fallen on the right hand in dorsiflexion and had received

no treatment Roentgenograms showed the old fracture of the right navicular bone at the junction of the middle and the outer third The slot graft operation was performed Postoperative roentgenograms showed one bone fragment in the soft parts Three months after the operation the patient worked without apparatus One year later he was free of symptoms, with a normal range of motion Roentgenograms showed deformity of the navicular bone, with apparent union

CASE 6—L G, a man aged 31, was admitted to the hospital on Jan 16, 1930 Three months before, in trying to arrest a thief, he had sustained a fracture of the right navicular bone Roentgenograms showed nonunion of the navicular bone A slot graft from the tibia was inserted In two months the patient discarded all apparatus and returned to work Fifteen months after the operation roentgenograms showed union of the bone through one-half its diameter The patient was free of symptoms, and his motions were normal

CASE 7—J C, a man aged 26, was admitted to the hospital on May 29, 1930 Eighteen months previously he had fallen on an outstretched hand, sustaining a fracture of the right navicular bone Roentgenograms showed nonunion The operation was an insertion of a tibial graft through a drill hole The patient discarded the apparatus and returned to work in two months Two and a half years later he was working full time, with the function normal and the fracture line indistinct The case is not classed as one of definite bony union

CASE 8—J H, a man aged 30, was admitted to the hospital in 1930 Five months previously he had fallen on an outstretched hand, sustaining a fracture of the right navicular bone Roentgenograms showed nonunion A slot graft from the tibia was inserted The patient discarded all apparatus and returned to work six weeks after the operation Two years later there was bony union The patient was working full time at his old job, and function was normal

CASE 9—M B, a man aged 28, was admitted to the hospital in 1930 He had fallen on an outstretched hand four months previously, receiving a fracture of the right navicular bone He had been given no treatment Roentgenograms showed nonunion A slot graft from the tibia was inserted The patient returned to work in six weeks without apparatus He left the country but wrote two years later that so far as he could determine his hand was absolutely normal

CASE 10—P D, a man aged 21, was admitted to the hospital on July 11, 1934 He had fallen on an outstretched hand nine months previously and had received no treatment Roentgenograms showed a fracture of the right navicular bone at the junction of the outer and the middle third A bone graft from the tibia was inserted through a drill hole The patient wore a plaster casing for eight weeks and a leather wristlet for an additional eight weeks At the end of eight months there were still pain and some limitation of motion Roentgenograms showed non-union

CASE 11—K K, a man aged 27, was admitted to the hospital on Feb 17, 1931 He had fallen on an outstretched hand sixteen months previously and had received no treatment Roentgenograms showed the old fracture of the right navicular bone at the junction of the middle and the outer third A bone graft from the tibia was countersunk into the navicular bone At the end of four years the patient was working normally without pain His motions were normal Roentgenograms showed some evidence of union, but it was not solid

CASE 12—J P, a man aged 21, was admitted to the hospital in January 1935. Two months before, he had fallen on an outstretched hand. He had received no treatment. There were still pain and weakness of the wrist. Roentgenograms showed fibrous union. A bone graft from the tibia was inserted through a drill hole. The patient wore a circular plaster for one month and a leather wristlet for an additional two months. Five months later roentgenograms showed bony union.

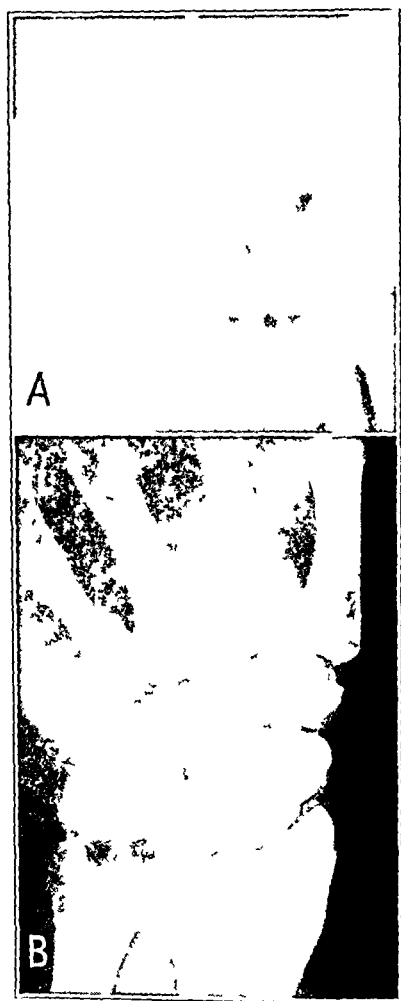


Fig 17 (case 13)—Bony union produced by autogenous graft in an eight year old fracture of the navicular bone. *A*, the wrist eight years after original injury, *B*, the wrist two years after autogenous graft, showing bony union, although there is still some vacuolation of the fragments.

CASE 13—F D, a man aged 27, was admitted to the hospital in September 1935. He had fallen on an outstretched hand eight years previously and had received no treatment. Roentgenograms showed nonunion of the navicular bone with cystic degeneration. A bone graft from the tibia was inserted through a drill hole. Two years later the patient stated he was working full time in a machine shop in New

Jersey There seemed to be "more bone" in the wrist, but it was stronger and there was very little pain. Motions were about two-thirds normal. Roentgenograms showed bony union (fig 17).

CASE 14—W K, a man aged 26, was admitted to the hospital in September 1934. He had fallen on a dorsiflexed hand six years previously while playing football. The wrist had been painful at intervals since the original injury. After a second fall, one year before admission, the pain increased. Roentgenograms showed nonunion of the navicular bone. A bone graft from the tibia was inserted through a drill hole. Six months later roentgenograms showed nonunion, with absorption of the graft. The patient is still wearing a wristlet. This case must be listed as a failure.

CASE 15—R T, a man aged 19, was admitted to the hospital on Feb 24, 1936. Six months before, the patient had injured his wrist while playing football. The injury was regarded as a sprain, and roentgenograms showed "no fracture." The pain had continued, and three months before admission the patient had been given a leather wristlet, which he wore intermittently. Roentgenograms showed a distinct fracture line with delayed union. The wristlet was not helpful. Roentgenograms on admission showed the old fracture at the junction of the proximal and the middle third, with nonunion. A bone graft from the tibia was inserted through a hole drilled through the distal and the proximal fragment. Postoperative roentgenograms showed the fragments in good position and the graft in a satisfactory position, although the graft extended slightly beyond the proximal portion of the navicular bone. There was bony union through the region of the graft. The patient was examined at the end of seventeen months. There were still thickening of the navicular bone and restriction of motion of the wrist to approximately two-thirds normal. There was occasional pain in the wrist when the patient struck a sudden blow. Roentgenograms showed union at the site of the graft but no evidence of union of the main portion of the fragments.

COMMENT

One fracture, that in case 14, was not improved by the operation, in this instance there was nonunion of six years. Possibly this fracture would have been better treated with excision of the entire navicular bone. In 2 cases, 10 and 15, there was only moderate improvement. The injured wrists in these 2 cases continued to have fairly marked limitation of motion, and pain when the wrist was forced to the limit of motion. In case 13 bony union was secured after eight years of nonunion. In another case the patient was free of symptoms and had a normal range of motion but the complete fracture line could be seen when the last roentgenograms were taken. In the remaining 8 cases either partial or complete bony union was produced and the patient was relieved as a result of the operation.

SUMMARY

An adequate knowledge of the relationship of the carpal bones is necessary for making accurate diagnoses of injuries to these structures. The importance of early diagnosis and adequate early treatment of carpal

navicular injuries is emphasized. Practically all navicular fractures heal if recognized and treated early by prolonged immobilization. For fractures in which nonunion of the navicular bone has developed as a result of delayed treatment, the introduction of an autogenous bone graft introduced through a drill hole in the bone followed by prolonged fixation in plaster seems to produce the most satisfactory results.

ABERRANT ADRENAL TUMOR OF UPPER PART OF ABDOMEN

REPORT OF A CASE WITH SIX YEAR CURE

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AND

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The following case is reported because of the unusual location of a large ectopic adrenal tumor and its successful surgical removal. Mention is made of similarly located tumors, and the early history of aberrant adrenal tissue in general is briefly given. Much of the literature concerning this subject is confusing because of the lack of proper classification. Frequently no clear distinction is made between malignant and benign nodules of adrenal tissue. The frankly malignant tumors of such origin are rare.

REPORT OF CASE

Clinical History—E R, a white married woman aged 51, was admitted to Ellis Hospital on March 29, 1933, with the chief complaint of intermittent attacks of nausea and vomiting. The family history seemed irrelevant except that the father had died of carcinoma of the colon at the age of 68.

The illness for which the patient sought relief had begun one year before admission, with an attack of nausea and vomiting. This attack was followed by similar attacks, coming in the beginning about once a month and then increasing in frequency. The duration of the attacks was short at first, but later in the illness they persisted for two or three days. The patient complained of a feeling of fulness and pressure in the epigastrium but had no pain. There was moderate constipation, but the stools were of normal color. There was slight loss of weight, and the appetite was poor. In the latter part of the illness the patient became aware of a mass in the upper part of the abdomen.

In 1924 roentgen therapy was given for uterine bleeding (2 milliamperes hours in divided doses), and menses ceased thereafter. In 1929 the patient complained of frequency of urination and a bearing-down sensation. Repeated urinalyses showed the urine normal, and the symptoms were promptly controlled by medication.

Physical Examination—The patient was well developed and fairly well nourished. The skin showed moderate pallor. The pulse, temperature and respirations were normal. Examination of the heart and lungs disclosed nothing unusual. The blood pressure was 140 systolic and 80 diastolic. The abdomen was soft and

From the Surgical Service, Ellis Hospital

not distended. There was a freely movable firm rounded mass in the upper and middle portion of the abdomen, slightly tender and about the size of a large orange. The liver and spleen were not palpable, and pelvic and rectal examinations gave negative results. There was no evidence of any secondary sexual changes suggesting virilism.

A roentgen examination of the stomach and small intestine disclosed no abnormality except decided ileac stasis. The colon showed no filling defects, but there was rapid emptying of the cecum. The abdominal mass appeared to be outside the gastrointestinal tract.

Laboratory Data—Three specimens of urine examined before operation were free of albumin and sugar and contained no red blood cells or leukocytes. A fourth

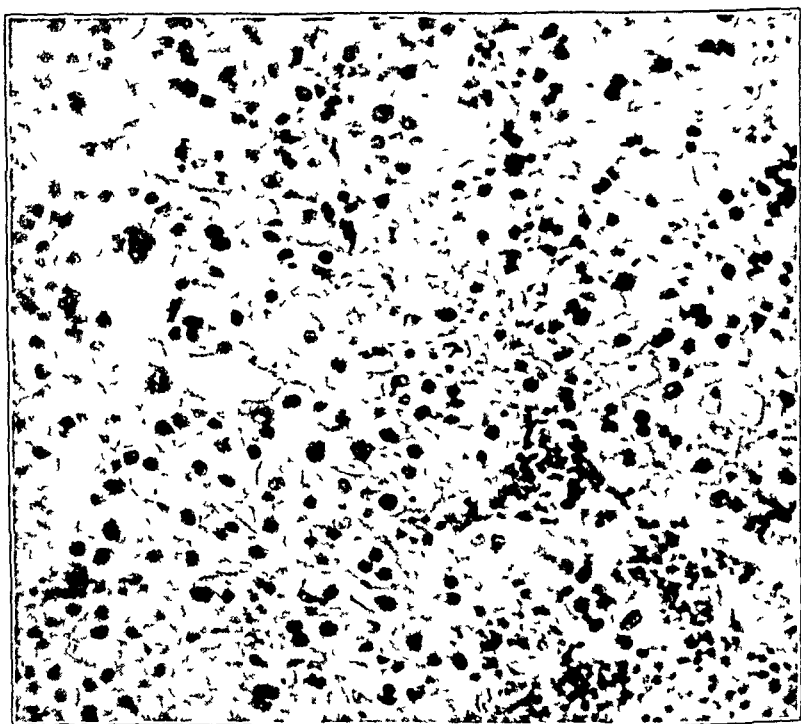


Fig 1—Aberrant adrenal carcinoma (low power)

specimen examined before operation was likewise free of albumin and sugar but contained a few red cells and white cells. A blood count revealed hemoglobin 61 per cent (Newcomer), red cells, 3,320,000, and white cells, 7,000, with polymorphonuclears 62 per cent, lymphocytes 28 per cent, endothelial leukocytes 5 per cent, eosinophils 3 per cent and basophils 2 per cent. The red blood cells were normal in size and shape. The urea nitrogen content of the blood was 9.5 mg and the sugar content 93.7 mg per hundred cubic centimeters. The Wassermann reaction of the blood was negative.

Operation and Course—After a preliminary blood transfusion an operation was performed on April 3, 1933, with the patient under spinal anesthesia. An upper right rectus incision disclosed a nodular mass approximately 6 by 10 cm in the

omentum just beneath and adherent to the middle of the transverse colon. The liver, the pouch of Douglas and the mesenteric lymph glands contained no nodules suggesting metastasis. The rest of the colon was normal. An attempt was made to separate the mass in the omentum from the transverse colon but had to be abandoned because of the danger of spilling the soft contents of the tumor. Instead, the tumor and the adherent portion of the colon were resected in one piece. The divided ends of the bowel were inverted and a lateral anastomosis was performed. The cecum, which was very mobile, was then sutured to the peritoneum at the lower angle of the wound, a potential cecostomy opening was thus established.

Three days after the operation it was necessary to open the cecum with a cautery to relieve distention and vomiting. On the fourth postoperative day fluids

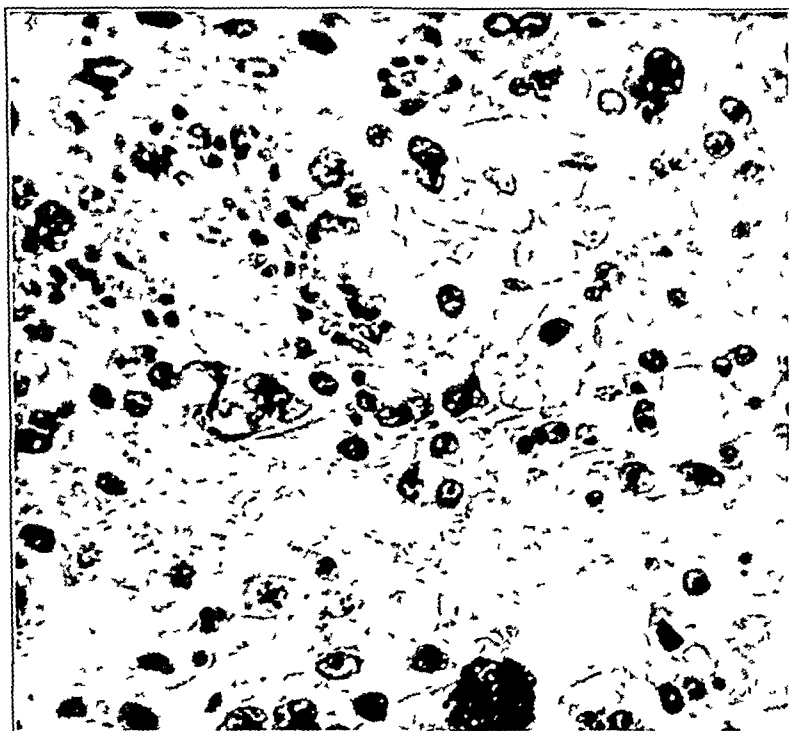


Fig 2—Aberrant adrenal carcinoma (high power)

were taken by mouth, and the postoperative course was uneventful thereafter. The patient was discharged fifteen days after the operation, with the operative wound healed and the cecostomy wound closing rapidly.

The tumor was an irregular globular mass measuring 6 by 7 by 10 cm. Its outer surface was nodular, capsulated and covered in part with small fat lobules. Several bluish nodules of tissue were seen beneath the serous surface. On section the mass appeared to be composed mainly of soft yellowish hemorrhagic tissue without definite structure. A narrow margin of grayish soft translucent tissue was found beneath the capsule. The piece of attached intestine, 45 cm long, was without evidence of tumor, and the mucosa was intact. Microscopic sections showed islands of tumor tissue surrounded by extensive areas of necrosis. The tumor cells

were large and somewhat polygonal and were best preserved about the vascular spaces. The cytoplasm was markedly granular or cribriform. Nuclei varied greatly in size, but the majority were large and rather pale, and mitotic figures were present. A diagnosis of hypernephroma (adrenal carcinoma) was made.

The patient has been in good health since operation. Repeated physical examinations and urinalyses have failed to show any evidence of recurrence.

LITERATURE

The terminology of ectopic, or misplaced, adrenal rests and of subsequently developing tumor has been a subject of much speculation since the work of Chiari¹ in 1884. Such tissue has been described by names like heterotropic hypernephroma, aberrant adrenals of Marchand and extrarenal hypernephroma.

The earliest descriptions were by Rokitsansky² in 1849, by Marchand³ in 1878, and by Chiari six years later. Apparently Chiari was the first to describe malignant transformation of such ectopic tissue located in the retroperitoneal space. Such adrenal rests have been described throughout the upper part of the abdomen, below the diaphragm and in the retroperitoneal space as low as the small pelvis in females and the scrotum in males. The embryologic development of these aberrant adrenal rests was thoroughly described by Broman⁴ in 1911. Glynn⁵ added materially to the subject in 1912, and made an even fuller study in 1921.

Nicholson⁶ in 1894 described an ectopic adrenal tumor found at autopsy, closely similar to the tumor in the case which we have reported. The mass measured 1.5 by 0.25 inches and was attached to the transverse mesocolon, the pancreas lying behind and above and the transverse colon in front. Microscopically this tumor proved to be an adrenal capsule. Evidently this tumor was found accidentally and was not malignant.

1 Chiari, H. Zur Kenntnis der accessorischen Nebennieren des Menschen, *Ztschr f Heilk* **5** 449-458, 1884.

2 von Rokitsansky, C. A Manual of Pathological Anatomy, translated by E. Sieveking, London, Sydenham Society, 1849, vol 2, p 244.

3 Marchand, F. Ueber accessorische Nebennieren im Ligamentum latum, *Virchows Arch f path Anat* **92** 11-19, 1883.

4 Broman, I. Normale und abnormale Entwicklung des Menschen, Wiesbaden, J. F. Bergmann, 1911, p 808.

5 Glynn, E. E. (a) The Adrenal Cortex, Its Rests and Tumors. Its Relation to Other Ductless Glands and Especially to Sex, *Quart J Med* **5** 57-192, 1912, (b) A Comparison Between Ovarian "Hypernephroma" and Luteoma and Suprarenal Hypernephroma, with Comments on Suprarenal Virilism, *J Obst & Gynaec Brit Emp* **28** 23-68, 1921.

6 Nicholson, B. S. Abnormal Position of Suprarenal Gland, *Brit M J* **1** 408, 1894.

Gynecologists, especially Glynn, have described such tumors in the small pelvis and the ovary Schiffmann in 1926⁷ and in 1930⁸ reported tumors arising in the female pelvis, the second of which invaded the mesentery He described the case of a 78 year old woman who complained of abdominal pain of two weeks' duration A tumor the size of a head filled the right side of the pelvis and displaced a small uterus to the left lower quadrant of the abdomen A diagnosis of intraligamentary tumor was made Operation disclosed a retroperitoneal tumor 11 by 12 by 16 cm, the upper pole of which protruded into the mesenteric root of the cecum The patient died three days later of cardiac insufficiency, and necropsy revealed a hypernephroid tumor of the lower pole of the left kidney which infiltrated the renal vein The foregoing case illustrates a fairly frequent condition in which the secondary tumor is obvious and the seemingly primary tumor obscure It is of interest that the upper pole of the pelvic tumor invaded the mesentery of the large bowel

An unusual case of adrenal virilism was described by Kolodny⁹ in 1934 A 37 year old woman noted a mass in the left epigastrium about twelve months before examination The tumor grew rapidly and was associated with digestive difficulty Menstruation had ceased about eight months before discovery of the tumor Examination disclosed a rather obese woman with coarse voice and features and with rough, red skin The distribution of the suprapubic hair was of definitely vertical (male) type The clitoris was twice the normal size A tumor the size of a child's head was located in the left side of the epigastrium Operation disclosed the tumor adherent to the abdominal wall, with the transverse colon tightly stretched over the inferior and the posterior aspect The tumor, which weighed 1,250 Gm, was located between the leaves of the transverse mesocolon in the region of the solar plexus The tumor was removed, and because of invasion of the stomach a Billroth I resection was necessary The sexual changes retrogressed after operation Six months after operation roentgenograms of the chest disclosed pulmonary metastasis, and one month later, or seven months after the operation, the patient died

SUMMARY

An unusual case of aberrant adrenal tumor in the upper part of the abdomen of a 51 year old woman which was successfully removed over six years ago is reported

7 Schiffmann, J, and Szamek, L Ein hypernephroides Sarkom im kleinen Becken, Arch f Gynak **127** 194-207, 1926

8 Schiffmann, J Hypernephroides Sarkom im Beckenbindegewebe, hypernephroides Sarkom der Niere, Arch f Gynak **144** 685-702, 1930

9 Kolodny, A Suprarenal Virilism in a Woman Tumor of an Extrarenal Suprarenal Rest, J A M A **102** 925-926 (March 24) 1934

Three cases are cited from the literature in which invasion of the mesentery occurred, in 2 of which cases the tumor was located in the upper part of the abdomen

NOTE—Attention should be called to the recent excellent article of Nelson¹⁰

Dr Charles G McMullen permitted us to report the case, and Dr Ellis Kellert supplied the photomicrographs

10 Nelson, A A Accessory Adrenal Cortical Tissue, Arch Path **27** 955 963 (June) 1939

CARCINOMA OF THE RECTUM AND OF THE RECTOSIGMOID IN THE YOUNG

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AND

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The factors which influence the prognosis of carcinoma of the rectum and of the rectosigmoid in persons 30 years of age and less are multiple, although at present the most satisfactory indicators are the ability of the patient to withstand the effects of surgical removal of the lesion and the presence or absence of metastasis. The latter factor closely parallels the grade of the tumor as classified by Broders¹. The clinical observations, the age and the sex of the patient and the rectal and proctoscopic observations, as well as the observations made at the time of surgical exploration, all must be correlated before the future health of a patient can be determined with any approximation of accuracy.

The present paper is a review of 116 cases of carcinoma of the rectum and of the rectosigmoid in which persons 30 years of age and less were involved. The patients were examined at the Mayo Clinic between the years 1910 and 1933, inclusive. Although the number of instances of this type of lesion seen annually since 1933 has increased, it was necessary for the purposes of this study to exclude all cases recorded at the clinic after 1933 so that a five year survival rate might be determined. It is of interest to notice that 3.4 per cent of the patients with carcinoma of the rectum and rectosigmoid who were treated at the Mayo Clinic between the years 1910 and 1933 inclusive were 30 years of age or younger. Phillips and Walters² recently reviewed the cases of carcinoma of the stomach at the Mayo Clinic in which the patients were 30 years of age or younger and found this group to constitute 2.4 per cent of the total number of patients with carcinoma of this organ.

In computing the statistics concerning patients who were operated on, we did not include in our calculations any patient who had not been traced for a period considered by us to be sufficient for the estimation

From the Division of Surgery, the Mayo Clinic

1 Broders, A. C. The Grading of Carcinoma, Minnesota Med 8 726-730 (Dec) 1925

2 Phillips, R. B., and Walters, W. Personal communication to the authors

of legitimate survival rates. Of the cases in which death occurred in the hospital and in which death was designated as "operative" or "hospital" none was included in computing the survival rate.

The part that clinical observations play in determining the curability of a lesion is not great, but when on rectal and proctoscopic examination a carcinoma has been found the prognosis depends on the operability of the lesion, which, in turn, depends on the grade of the lesion and the general condition of the patient. Age is another factor which influences the prognosis. Although the lesions of the young persons in our series were found to be of a higher grade than is usual among older patients, we did not find justification for the hopeless outlook taken by some authors for this group of patients. Young patients, as a rule, withstand surgical procedures well. Because of this, the percentage of young patients who are acceptable for radical operative procedures is greater than that of older patients who are acceptable for the same procedures. In 56 per cent of the cases studied, some form of resection of the lesion had been performed as a curative procedure and not for palliation.

It is generally believed that the operative risk accompanying resection of the rectum is less among females than among males, largely because the width of the female pelvis is greater than that of a male, a fact which renders mobilization of the female rectum easier and, in consequence, lessens the risk of sepsis. In this study, all patients in whom anterior resection of rectal lesions was undertaken were women. This accounts in a large measure for the higher operative mortality rate among women. The numbers of patients of the two sexes were about equal, 51 per cent of the patients being males and 49 per cent being females. Ninety per cent of the "hospital deaths" in the group of cases in which resection was performed occurred among women.

Rectal and proctoscopic examinations made diagnosis possible in 100 per cent of the cases in this study. In addition to permitting a diagnosis of carcinoma, examinations enabled other factors to be learned which aided in formulating a prognosis. As a rule, the smaller, the more protuberant and the more movable the lesion, the more likely it is that satisfactory and complete resection may be performed, although Gilchrist and David,³ after analysis of 22 specimens, concluded that the size of the tumor is of little value in determining the presence or absence of metastasis to lymph nodes. Tumors which are questionably operable because of their size may not involve lymph nodes, and, conversely, small tumors may show extensive involvement of lymph nodes. There is one type of carcinoma of the rectum which is recognizable grossly and which usually is of a low grade of malignancy and unlikely to

3 Gilchrist, R. K., and David, V. C. Lymphatic Spread of Carcinoma of the Rectum, *Ann Surg* 108 621-642 (Oct) 1938

metastasize, this is the "papilliferous carcinoma," classed as the type of growth which protrudes into the lumen of the rectum. The aforementioned qualities characterizing this lesion were found to be present among those patients in our series who had the lesion and are also observations which have been noted by Dukes,⁴ McVay⁵ and Hayes.⁶ Lesions situated anteriorly in the rectum, particularly perforating lesions, have a poorer prognosis than have similar lesions situated on the posterior rectal wall, for the reason that such anterior lesions commonly involve other viscera. Removal of lesions of the anterior rectal wall entails added risk. Gilchrist and David found more lesions with metastasis among those situated on the mesenteric border of the bowel than among those arising on the antimesenteric border. Westhues⁷ has pointed out that fixation to the sacrum or to the prostate gland is caused more often by inflammatory reaction than by the carcinoma itself, and his conclusion should be considered before a tumor with such fixation is called "inoperable."

The situation of the tumor is of importance from the standpoint of prognosis, because of the difference caused by it in the time of appearance of symptoms, the grade of the tumor and the channels by means of which metastasis occurs. Tumors situated near the external anal orifice usually are epitheliomatous and for the most part follow the lymphatic vessels which drain toward the inguinal glands. When these are involved, the lesion is rendered inoperable by anything other than a palliative procedure. Low-lying lesions may have high metastases, as has been shown by Gilchrist and David, and such metastases usually follow the lymphatic chain along the superior hemorrhoidal artery. Because of this, high ligation of the artery and the accompanying lymphatic vessels should be carried out when possible. When the lesion is situated in the lower or the middle third of the rectum, a sufficiently accurate estimate of its mobility can be made by the examining finger. When the lesion is situated higher than the aforementioned structures, particularly when it is in the rectosigmoid region, the accuracy of determining its operability is practically nil.

The advisability of attempting to determine the degree of fixation and situation of the lesion by manual and proctoscopic examination has been questioned, and justifiably so. Rectosigmoid growths often

4 Dukes, C. E. The Classification of Cancer of the Rectum, *J. Path. & Bact.* **35** 323-332, 1932

5 McVay, J. R. Involvement of the Lymph-Nodes in Carcinoma of the Rectum, *Ann. Surg.* **76** 755-767 (Dec.) 1922

6 Hayes, J. M. The Involvement of the Lymph Glands in Carcinoma of the Large Intestine, *Minnesota Med.* **4** 653-663 (Nov.) 1921

7 Westhues, H. Die pathologisch-anatomischen Grundlagen der Chirurgie des Rektumkarzinoms, Leipzig, Georg Thieme, 1934

telescope themselves into the lower part of the rectum and physically appear to be fixed, but on exploration the lesion will be found to be freely movable and situated at a much higher level. In the present study, 28 per cent of the resected lesions had been described as "fixed" on proctoscopic and manual examination, 34 per cent had been recorded as being attached or having limited motion and 38 per cent had been recorded as freely movable. Among younger persons as well as the older group, lesions situated high in the rectum or rectosigmoid had a poorer prognosis from the standpoint of operability, because they usually required some type of combined abdominoperineal resection or anterior resection, both of which procedures carry a higher operative risk than does posterior resection. In addition to the higher operative mortality in cases of high-lying tumors, the duration of life in these instances also was decreased. The average duration of life in cases in which resection was performed for lesions of grade 2 or grade 3 situated in the upper third of the rectum or in the rectosigmoid was three and two-tenths years. The average duration of life in a similar group of cases in which the lesions were situated in the lower third of the rectum was five and eight-tenths years. In neither group were deaths in the hospital included in the calculations.

The prognosis based on exploratory laparotomy was, generally speaking, more nearly accurate than that based on clinical examination and proctoscopic observations. This increase in accuracy was most noteworthy in cases of high-lying lesions, particularly in patients having a small pelvis. The mobility of the tumor, the presence or absence of regional and visceral metastasis and the presence of free fluid in the abdomen all provide valuable information as to operability of the lesion.

Although gross examination of the lymph nodes at the time of exploration may be used as a rough guide to operability, it should not be the determining factor as to whether a curative or a palliative procedure should be performed. Some of the largest glands removed at the time of exploration were found on histologic examination to be inflammatory. Gabriel, Dukes and Bussey,⁸ on examining 1,242 lymph nodes, made a study as to the accuracy of gross examination of the nodes. Of 1,242 nodes, the appearance of 905 was considered on the basis of gross characteristics to be normal, but subsequent microscopic examination showed 18 to contain metastasis, an error of 2 per cent. Of 337 nodes of which the appearance was judged to indicate malignant involvement on the basis of gross characteristics, metastasis was present in only 132—an error for 265, or 61 per cent, of the total number of nodes. The commonest error in our cases was that of presuming nodes to be

8 Gabriel, W. B., Dukes, C., and Bussey, H. J. R. Lymphatic Spread in Cancer of the Rectum, *Brit J Surg* 23:395-413 (Oct.) 1935.

involved by metastasis when in reality the enlargement was due to inflammatory involvement. Although the prognosis when involvement of the nodes is present is, as a rule, poorer than when it is absent, our study showed that a certain proportion of patients do survive the five year period and that, although a more radical operation may be necessary, something more than a palliative procedure should be instituted. Of the patients for whom resection was performed, 62 per cent were found by histologic examination to have nodular involvement. Brown and Warren⁹ found the lymph nodes to be disappointing indicators as to prognosis for carcinoma of the rectum, because visceral metastasis often occurs independently of neoplastic lymph nodes. It would appear that local growth often provides a clue as to the possibility of visceral metastasis, since evidence of invasion of the blood vessels was noted on histologic examination of several of our patients. It is well to remember, however, that many such instances were encountered in which no evidence of visceral metastasis was noted. Warren and Gates¹⁰ have shown experimentally that only a small proportion of tumor cells entering the blood stream become manifest as visceral metastasis. Clute and Warren¹¹ have shown the same thing concerning the thyroid gland, in which intravascular invasion of a malignant lesion frequently is noted but in which distant metastasis rarely is seen.

PROGNOSIS BASED ON PATHOLOGIC INVESTIGATION

Carcinoma of the rectum may be subdivided into numerous gross forms, such as polypoid carcinoma and mucoid papillary carcinoma, but this is often misleading. Broders¹² stated that such a classification is unnecessary and confusing and chose to classify the forms under the general term "adenocarcinoma."

The tumors of this series were graded as suggested by Broders because the value of this method of grading has been demonstrated on numerous occasions (table 1).

Of the patients with grade 1 carcinoma subjected to some form of curative operation, 75 per cent survived the five year period. There was a decrease of 28 per cent for the next grade, and only 10 per cent of the patients with grade 3 tumors survived the five year period. As the grade of malignancy increased, the percentage of five year cures decreased.

9 Brown, C. E., and Warren, S. Visceral Metastasis from Rectal Carcinoma, *Surg., Gynec. & Obst.* **66** 611-621 (March) 1938.

10 Warren, S., and Gates, O. The Fate of Intravenously Injected Tumor Cells, *Am. J. Cancer* **27** 485-492 (July) 1936.

11 Clute, H. M., and Warren, S. Cancer of the Thyroid Gland, *Am. J. Cancer* **15** 2563-2582 (Oct.) 1931.

12 Broders, A. C., cited by Buie¹⁴ p. 378.

The data in table 2 are in agreement with those of other reports¹³ which support the contention that carcinoma in young persons is usually of a higher grade than in older persons. We encountered 1 case at the clinic, however, in which a child 2½ years of age had a large bleeding polyp situated in the upper third of the rectum. This polyp was found to be an adenocarcinoma of grade 1. The lesion was fulgurated, and the patient was living and well nine years later (table 2).

TABLE 1—Cases in Which Operations for Cure Were Performed. Grades of Tumors, Percentages of Cases in Each Grade and Percentage of Five Year Survival

Grade (Broders)	Percentage of Cases	Percentage of Survival
1	12.0	75
2	50.0	47
3	30.9	10
4	7.1	*

* One patient lived fifteen years. The other patients died within an average of eight months after the operation. Cases of "operative death" or death in the hospital are not included.

TABLE 2—Grades of Lesions and Percentage of Cases of Each in a Total Group of 116 Cases of Carcinoma of the Rectum and Rectosigmoid in Patients Under 30 Years of Age

Grade (Broders)	Percentage
1	11.7
2	46.7
3	26.6
4	15.0

TABLE 3—Grades of Tumor. 2,723 Cases of Carcinoma of the Rectum in Persons of All Age Groups*

Grade (Broders)	Percentage of Cases
1	45
2	39
3	15
4	1

* As studied by L. A. Buie

Table 3 represents the findings of Buie,¹⁴ who reviewed 2,713 cases of carcinoma of the rectum involving patients of all ages, carcinoma had

13 Brindley, G. V. Carcinoma of the Rectum. Factors Affecting Its Cure, J. A. M. A. **108** 37-43 (Jan 2) 1937. Shedden, W. M. Carcinoma of the Rectum and Sigmoid with Particular Reference to the Disease as Seen in Youth, New England J. Med. **209** 528-539 (Sept.) 1933. Fowler, L. H. Malignant Epithelial Neoplasms, Carcinoma and Epithelioma, Occurring in Persons Under Twenty-Six Years of Age, Surg., Gynec. & Obst. **43** 73-84 (July) 1926.

14 Buie, L. A. Practical Proctology, Philadelphia, W. B. Saunders Company, 1937.

been diagnosed on proctoscopic examination and had been confirmed by histologic means. It will be noted that a greater percentage of high grade tumors occurs in patients under 30 years of age than in older patients. By comparing tables 2 and 3, one sees that among persons less than 30 years of age a greater percentage of the lesions are of grades 2 and 3, whereas in the group which includes all ages, represented in table 3, a greater percentage of the lesions are of grades 1 and 2 than of the other two grades.

The type of surgical procedure employed not only affects the immediate mortality (hospital mortality) but in a measure determines the curability of the patient. The type of operation to be employed rests on an analysis of a number of factors, namely, the age of the patient, the situation and grade of the lesion, the duration of symptoms and the general condition of the patient. A young patient is fortunate from every standpoint if the lesion is situated low in the rectum. In the analysis of the present series of cases, patients with lesions situated low in the rectum for which some form of posterior resection was performed were found to have an average postoperative life of five and eight-tenths years, with an operative mortality of only 2.7 per cent. The combined operative mortality for the entire group of patients treated by resection was 12.3 per cent.

SUMMARY AND CONCLUSIONS

A series of 116 cases of carcinoma of the rectum and of the rectosigmoid in persons 30 years of age and less, observed from 1910 to 1933 inclusive, was studied.

Lesions situated high in the rectum or rectosigmoid have a poorer prognosis from the standpoint of operability as well as from the standpoint of duration of life.

The prognosis based on exploratory laparotomy is superior to that based on clinical examination.

The grade of the tumor as determined by Broders' classification and the presence or absence of local or visceral metastasis are the most important aids in establishing an accurate prognosis. The incidence of visceral and local metastases closely parallels the grade of the original lesion.

ANKLE FUSION FOR CORRECTION OF PARALYTIC DROP FOOT AND CALCANEUS DEFORMITIES

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Recent reports have been published concerning the treatment of paralytic drop foot by means of posterior bone block operations. Admittedly, an appreciable percentage of unsatisfactory results has followed the use of this procedure.¹ Posterior bone block for paralytic drop foot was tried at the New York Orthopaedic Dispensary and Hospital, but the results were not satisfactory. Accordingly, the procedure was abandoned. Ankle fusion was adopted and has been used extensively for both drop foot and calcaneus deformities.

During the five year period from 1934 to 1938 inclusive 106 ankle fusions were done in this hospital for the correction of paralytic deformities resulting from anterior poliomyelitis. Ankle fusion was done in 72 instances to correct drop foot deformity and in 34 instances to correct calcaneus deformity. The patients have been observed from year to year in the follow-up clinic, and the end results have been gratifying.

DROP FOOT

Among the 72 patients in whom ankle fusion was done to correct drop foot deformity, there were 52 females and 19 males. Their ages at operation ranged from 8 to 39 years, the majority being in the second decade. In 66 instances a subtalar triple arthrodesis had been done previously because of concurrent lateral instability of the foot caused by varus or valgus deformity. The involved extremities presented from $\frac{1}{4}$ to $2\frac{1}{2}$ inches (0.64 to 6.2 cm) of shortening, in 3 instances the leg was $\frac{1}{4}$ inch (0.64 cm) longer than its fellow.

Twenty-three patients with a paralytic drop foot also had an unstable knee because of partial or complete paralysis of the quadriceps femoris muscle. After ankle fusion with the foot in the proper degree of equinus, 19 of the 23 knees were stabilized so that no external support (in the form of the hand held over the knee or a long leg brace) was necessary. Two of the 4 patients in whom the knee was not stabilized after ankle fusion presented marked relaxation and recurvation at the involved knee and will require knee fusion for stabilization. In a case

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1 Carrell, W. B., and Childress, H. M. Posterior Bone Block in Talipes Equinus. Some Factors Determining the End-Results, *South M. J.* 32: 528 (May) 1939.

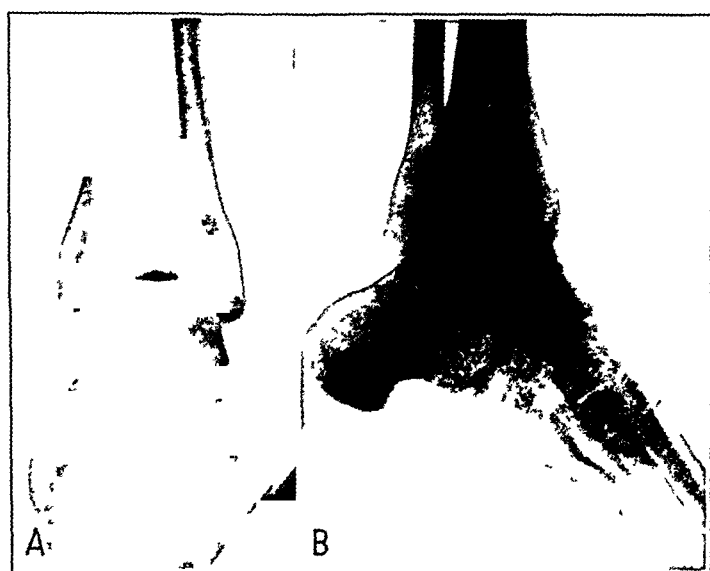


Fig 1—Preoperative anteroposterior views of a drop foot deformity due to anterior poliomyelitis *A*, anteroposterior view, *B*, lateral view A subtalar triple arthrodesis had been performed previously

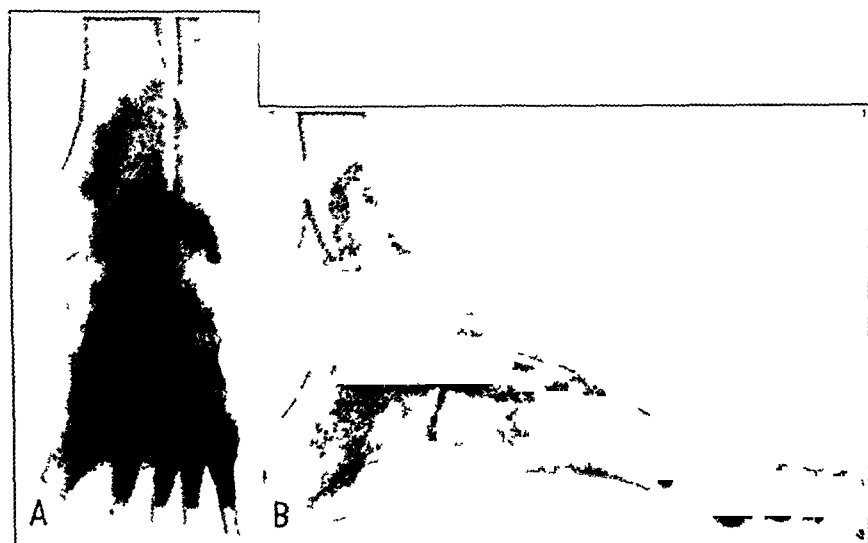


Fig 2—*A*, anteroposterior view and *B*, lateral view of the ankle shown in figure 1, twelve weeks after ankle fusion The ankle was solidly fused at 99 degrees of dorsiflexion

of drop foot with associated instability of the knee, it is wise to make a preoperative decision whether ankle fusion will successfully stabilize the knee, this is true also of an instability of the knee associated with calcaneus. To determine this, a short leg plaster walking cast is applied with the foot in approximately 10 degrees of equinus. If this renders the knee stable, fusion of the ankle in the proper degree of equinus will do likewise.

The amount of equinus was measured on the lateral roentgenogram by the intersection of a line drawn parallel to the long axis of the tibia and another line drawn from the plantar surface of the first metatarsal head to the plantar surface of the os calcis. Ten ankles were fused at 92 to 95 degrees of dorsiflexion, 29 at 95 to 100 degrees, 22 at 100 to 105 degrees, 10 at 105 to 110 degrees and 1 at 112 degrees.

In 62 of the 72 cases the end results were considered good. In 1 the ankle was fused in too much equinus (112 degrees of dorsiflexion), and in another, in not enough equinus (92 degrees of dorsiflexion). In 2 cases there was need of a subtalar triple arthrodesis because of "fore foot drop" and lateral instability. In 2 cases a revision of the existing subtalar triple arthrodesis was needed. Four patients were relieved of the drop foot deformity but continued to have an unstable knee.

CALCANEUS DEFORMITY

There were 34 cases of ankle fusion to correct calcaneus deformity. Twenty-two of the patients were males and 12 were females. Their ages at operation ranged from 8 to 44 years, the majority being in the second or third decade. In 31 patients of this group a subtalar triple arthrodesis had been previously done because of lateral instability or cavus deformity of the foot. The involved extremities presented from $\frac{1}{2}$ to $3\frac{1}{4}$ inches (12 to 82 cm) of actual shortening, in 1 instance the leg was $\frac{5}{8}$ inch (19 cm) longer than its fellow.

Nine patients with a paralytic calcaneus deformity also had an unstable knee. In 8 of these the knee was stabilized by ankle fusion. In 7 instances the ankles were fused at 90 to 95 degrees of dorsiflexion, in 17 at 95 to 100 degrees and in 10 at 100 to 105 degrees.

Of these 34 cases, the end results in 23 were considered good. In 8 the ankles were fused in not enough equinus (90, 90, 92, 94, 95, 98, 99 and 99 degrees of dorsiflexion). In 2 cases a subtalar triple arthrodesis was needed because of cavovalgus deformity of the foot. One patient was relieved of the calcaneus deformity but continued to have an unstable knee.

OPERATIVE PROCEDURE AND POSTOPERATIVE CARE

The anterior approach is used for arthrodesis of the ankle. An intra-articular fusion is done, tibial bone chips being used to promote osteogenesis. Care is taken to avoid exposure of or injury to the lower



Fig 3—Preoperative lateral view of a drop foot deformity (with associated instability of the knee) due to anterior poliomyelitis

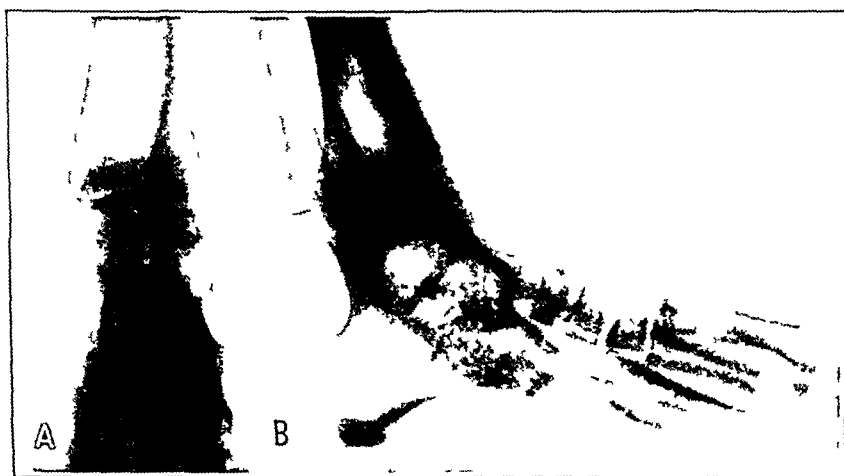


Fig 4—*A*, anteroposterior view and *B*, lateral view of the ankle shown in figure 3, nineteen months after ankle fusion (preceded by subtalar triple arthrodesis). The ankle was solidly fused at 102 degrees of dorsiflexion. The knee was stable. The lower tibial and fibular epiphyseal lines were still open.

tibial epiphysial cartilage The technic of the operative procedure has been recently described by Liebolt ²

A long leg plaster cast is applied with the foot in the estimated proper degree of equinus Care must be taken to see that the front part of the foot is in the maximum degree of dorsiflexion on the rear part, as this is its weight-bearing position Postoperative roentgenograms will determine the degree of equinus If it is too great or too little it can be corrected by wedging the cast Theoretically, it is better to err in the direction of too much equinus, since wedging into more dorsiflexion will serve to occlude the joint space further (Of the 106 cases, postoperative wedging was done in 27 All 27 ankles went on to solid bony union in the usual time, and in no case did delayed union result from the postoperative wedging) At the end of six weeks, weight bearing in a short walking cast is allowed At the end of another six weeks the cast is removed and the solidity of the fusion is checked with roentgenograms The shoe can then be adjusted if necessary Lifts in the heel or in the heel and sole can compensate for any shortening of the extremity and for the equinus of the foot If the ankle has been fused in too little equinus and there is associated instability of the knee, a metatarsal bar on the sole of the shoe is of benefit

Of the 106 cases in which operation was done, solid arthrodesis was obtained in 102 In 92 the ankles were solidly fused at the end of twelve weeks, in 10, additional periods of one to eight weeks were required before solid bony ankylosis resulted Four ankles (3 drop-foot deformities and 1 calcaneus deformity) failed to fuse solidly, an incidence of 4 per cent of pseudarthroses All four subsequently were solidly arthrodesed by a second operation Only one ankle fusion was revised The ankle was solidly fused but was reoperated on in order to obtain more equinus, which was needed to stabilize the knee

PROPER DEGREE OF EQUINUS

The success of the procedure depends largely on arthrodesing the ankle in the proper degree of equinus Factors to be taken into consideration are

- 1 Sex of the patient Women's high-heeled shoes require more equinus than do men's low-heeled ones
- 2 Degree of shortening of the involved extremity, if any
- 3 Presence or absence of associated instability of the knee

An excellent way to determine before operation the degree of equinus desired is to take a lateral roentgenogram with the patient standing while wearing a shoe with the heel height of his or her choice This

² Liebolt, F L Pantalar Arthrodesis in Poliomyelitis, *Surgery* 6 31 (July) 1939



Fig 5—Preoperative lateral view of a foot and ankle with a calcaneus deformity (with associated instability of the knee) due to anterior poliomyelitis. A subtalar triple arthrodesis had been performed previously.

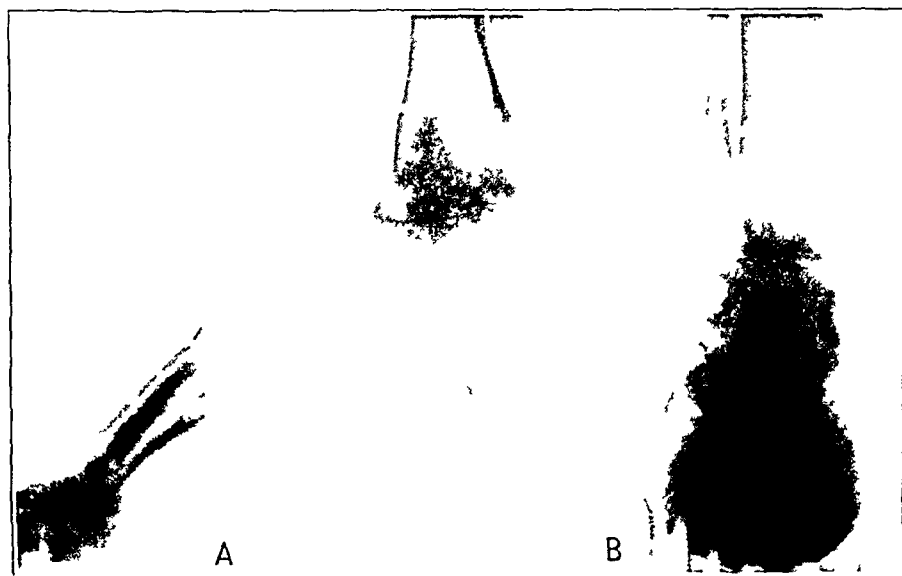


Fig 6—*A*, lateral view and *B*, anteroposterior view of the ankle shown in figure 5, twelve weeks after ankle fusion. The ankle was solidly fused at 98 degrees of dorsiflexion. The knee was stable.

applies to simple drop foot or calcaneus deformity. The plaster equinus boot test is more accurate when there is an unstable knee, the lateral roentgenogram of the foot and ankle in the equinus boot gives the desired degree of equinus.

In general, it is felt that the best functional position is 5 to 10 degrees of equinus for men and 10 to 15 degrees for women.

COMMENT

Ankle fusion for the correction of drop foot or calcaneus deformity is mechanically sound and is relatively simple technically. In this series of 106 cases there was no disturbance of growth, nor should there be any such disturbance with proper operative care. Arthrodesis of the ankle joint does not impair normal function of the extremity. If the ankle has been fused in the proper degree of equinus, it is often difficult or impossible to say which ankle has been arthrodesed by simply watching a patient walk and observing his gait. Any noticeable limp is usually due to concurrent muscular imbalance or to inequality in the length of the legs. It is true that after ankle fusion a patient's gait is usually poorer without shoes than with shoes on. However, the excellence of his gait with his shoes on more than offsets this disadvantage.

If a subtalar triple arthrodesis is to also be done, it should be done first, then, with the subsequent ankle fusion, the foot can be more accurately aligned with the leg to obtain the optimum degree of desired equinus.

SUMMARY

One hundred and six ankle fusions were done in a five year period (1934 to 1938 inclusive) on patients with residual anterior poliomyelitis at the New York Orthopaedic Dispensary and Hospital. Of these, 72 were done for paralytic drop foot and 34 for paralytic calcaneus deformities. The patients have been carefully followed, the follow-up period ranging from seven months to five and one-half years. In 85 cases (80 per cent) the end result was good. In 10 (9 per cent) the end result was only fair, there being either too much or too little equinus. In 5 (5 per cent) the end result was good so far as the ankle was concerned but an associated unstable knee was not rendered stable. In 6 (per cent) the end result was good so far as the ankle was concerned but an associated lateral instability of the foot needed further operative stabilization of the subtalar and midtarsal joints. In no case were the results considered poor. Of 32 unstable knees, 27 (84 per cent) were stabilized by ankle fusion. There was no resulting inter-

3 Turner, H. Deformities of Foot Associated with Arthrodesis of Ankle Joint Performed in Early Childhood, *J. Bone & Joint Surg.* **16** 423 (April) 1934

ference with growth in any case. Functional use of the involved extremity was improved in all cases. In 4 cases (4 per cent) pseudarthrosis developed, but in all 4 the joint became solidly arthrodesed after refusion.

CONCLUSION

Ankle fusion is a satisfactory method of treating drop foot and calcaneus deformities regardless of the cause. It results in freedom from disability caused by deformity, pain or instability. In a fused ankle there is no pain, bony impingement or swelling such as occurs at times after bone block operations. The operative procedure is relatively simple in contrast to such methods as the Lambrinudi operation⁴ and its modifications. An additional advantage is that associated instability of the knee can often be corrected by ankle fusion. The end results are uniformly satisfactory as indicated by this five year study of 106 cases.

It is important to avoid injury to the epiphysial cartilages of the distal ends of the tibia and fibula if they are still present. The end result is determined by the degree of equinus obtained. Five degrees to 10 degrees of equinus for males, and 10 to 15 degrees of equinus for females is in general satisfactory.

⁴ Lambrinudi, C. New Operation on Drop-Foot, *Brit J Surg* **15** 193 (Oct) 1927

EXPERIMENTAL GOITER DUE TO CALCIUM

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WICHITA, KAN

Until recently, endemic goiter was regarded as a deficiency disease due to lack of iodine in food and drinking water. Newer studies have called attention to the importance of positive goitrogenic factors.

The observation of Webster, Clawson and Chesney¹ that feeding cabbage to rabbits causes goiter in a short time proved that a dietary factor much more powerful than any iodine deficiency may be responsible for goiter.

During the last few years, another positive goitrogenic agent has been demonstrated. Using lime, calcium chloride or calcium carbonate in conjunction with a diet low in iodine, Tanabe,² Hellwig,³ Thompson⁴ and Hibbard⁵ produced goiters in white rats.

In experiments during 1929 and 1932 I was unable to obtain hyperplasia of the thyroid in white rats by lack of iodine alone. I concluded that iodine deficiency by itself cannot be the essential cause of endemic goiter and that there must be, rather, a positive goitrogenic agent. My standpoint was supported by Hibbard's⁵ experiments in a nonendemic region. In a recent paper, Kenyon⁶ objected to my conclusions and pointed out that Remington and Levine,⁷ Krauss and Monroe⁸ and

From the Department of Pathology, St Francis Hospital

1 Webster, B., Clawson, T. A., and Chesney, A. M. Endemic Goiter in Rabbits, Bull Johns Hopkins Hosp **43** 278, 1928

2 Tanabe, H. Experimenteller Beitrag zur Aetiologie des Kropfes, Beitr z path Anat u z allg Path **73** 415, 1925

3 Hellwig, C. A. Iodine Deficiency and Goiter. Influence of Diet Poor in Iodine on Thyroid Gland in White Rats, Arch Path **11** 709 (May) 1931, Experimental Goiter. Functional, Chemical and Histological Studies, *ibid* **19** 364 (March) 1935

4 Thompson, J. Influence of the Intake of Calcium on the Thyroid Gland of the Albino Rat, Arch Path **16** 211 (Aug) 1933

5 Hibbard, J. S. Experimental Thyroid Hyperplasia. Increased Intake of Chloride Combined with Diet Deficient in Iodine as Factor, Arch Surg **26** 648 (April) 1933

6 Kenyon, A. T. Histological Changes in Thyroid Gland of White Rat Exposed to Cold, Am J Path **9** 347, 1933

7 Remington, R. E., and Levine, H. Studies on the Relation of Diet to Goiter, J Nutrition **11** 343, 1936

8 Krauss, W. E., and Monroe, C. F. Comparison of Influence of Iodized Milk and of Potassium Iodide Administered Directly on Size and Iodine Content of Thyroid Gland of Rats, J Biol Chem **89** 581, 1930

Hayden, Wenner and Rucker⁹ have reported hyperplasia of the thyroid occurring in white rats on a diet deficient in iodine. An analysis of the goitrogenic diets used by these authors reveals, however, that they contained, without exception, an abundance of calcium.

Since my first successful attempts to produce goiter in white rats with calcium, the studies of Hibbard,⁵ Thompson⁴ and Stiner¹⁰ have brought up new questions. Hibbard⁵ produced hyperplasia of the thyroid by giving calcium chloride, while calcium lactate was without effect. He therefore expressed the opinion that the chlorine ion rather than the calcium ion is responsible for the development of goiter. Thompson⁴ found that the thyroids of rats fed a goitrogenic diet for longer than three months underwent secondary atrophy. At the first International Goiter Conference, Stiner¹⁰ stated that lack of vitamins is an important factor in the etiology of goiter.

It seemed advisable to repeat my experimental studies under conditions which would take into consideration the three questions which arose from the work of Hibbard,⁵ Thompson⁴ and Stiner¹⁰. 1. Is calcium carbonate as effective in producing hyperplasia of the thyroid as calcium chloride? 2. Does a prolonged experimental feeding reduce the size of the thyroid? 3. Does addition of vitamins to the goitrogenic diet prevent goiter?

EXPERIMENTAL DATA

The recent experiments were begun on Sept. 12, 1938, with 40 male white rats. All the animals were of the same age, 16 weeks, and approximately of the same weight. They were housed in lots of 10 in Dorrer cages which had floors of mesh wire. In order to maintain the utmost cleanliness no hay or other material was used for bedding. The cages were kept in a well lighted room at a constant temperature of 20 C to prevent any effect on the thyroid of darkness or low temperature. The experimental diet for each animal consisted of yellow corn meal (7 Gm), rolled oats (2 Gm), calcium carbonate (0.3 Gm), sodium chloride (0.1 Gm) and tomato juice (1 cc). Ten animals (series 1) received this diet with pure drinking water. Thirty animals (series 2) were given the same food, but as drinking water they were given a 2 to 10,000,000 solution of potassium iodide. This corresponded to a daily intake of 2 micrograms of potassium iodide for each animal. Groups of experimental animals were killed with chloroform three, five and eight months after the beginning of the feeding.

The thyroids were dissected immediately after death, measured and at once preserved in a 10 per cent concentration of solution of formaldehyde U. S. P. After embedding in paraffin, the cervical organs were cut in horizontal plane, and the sections that included the isthmus and both lobes of the thyroid were selected for microscopic study.

9 Hayden, E. M., Wenner, W. T., and Rucker, C. W. Production of Goiter in Rats by Restricted Iodine Feeding, *Proc. Soc. Exper. Biol. & Med.* **21**: 546, 1924.

10 Stiner, O. Zur Verbreitung des endemischen Kropfes in der Schweiz. in *Compte rendu Conference Internationale du Goitre*, Berne, Hans Huber, 1928, p. 403.

RESULTS

From tables 1 and 2 it is evident that the diet rich in calcium produced a definite enlargement of the thyroid. No decrease in size of the gland was noticed in animals fed such a diet for five and eight months. The animals of the first series showed large goiters with marked

TABLE 1 (Series 1)—Results Obtained with Male White Rats Fed Yellow Corn Meal, Rolled Oats, Calcium Carbonate, Tomato Juice and Pure Water

Rat	Weight, Gm	Duration of Experiment, Months	Size of Thyroid, Mm	
			Right Lobe	Left Lobe
1	230	3	8 by 3 by 2	7 by 4 by 2
2	225	3	7 by 2 by 3	7 by 3 by 4
3	130	3	7 by 3 by 3	7 by 2 by 3
4	140	3	7 by 4 by 2	6 by 3 by 2
5	116	3	7 by 3 by 2	6 by 3 by 2
6	145	5	6 by 4 by 2	7 by 4 by 2
7	115	5	5 by 4 by 2	6 by 4 by 2
8	222	5	7 by 4 by 3	7 by 4 by 3

TABLE 2 (Series 2)—Results Obtained with Male White Rats Fed Same Calcium-Rich Diet Supplemented with 2 Micrograms of Potassium Iodide Daily

Rat	Weight, Gm	Duration of Experiment, Months	Size of Thyroid, Mm	
			Right Lobe	Left Lobe
1	260	3	6 by 3 by 2	6 by 2.5 by 2
2	250	3	6 by 3 by 2	6 by 3 by 2
3	160	3	7 by 3 by 2	6 by 3 by 2
4	230	3	8 by 3 by 2	7 by 4 by 2
5	255	3	6 by 4 by 2	7 by 4 by 2
6	118	5	6 by 2 by 1.5	6 by 3 by 2
7	220	5	8 by 4 by 2	9 by 4 by 2
8	145	5	6 by 3 by 1.5	6 by 4 by 2
9	155	5	8 by 3 by 2	7 by 3 by 2
10	156	8	5 by 3 by 1	6 by 2 by 1
11	140	8	6 by 3 by 2	6 by 2 by 2
12	130	8	6 by 2 by 3	6 by 3 by 2
13	156	8	6 by 3 by 2	6 by 3 by 2
14	150	8	6 by 3 by 2	6 by 3 by 2
15	140	8	6 by 3 by 2	6 by 3 by 2
16	240	8	7 by 4 by 3	6 by 2.5 by 3
17	144	8	7 by 4 by 2	6 by 3 by 2
18	138	8	5 by 3 by 2	7 by 3 by 2
19	244	8	8 by 4 by 3	6 by 3 by 2

hyperemia. The size of the centrally located acini was between 30 and 40 microns. The lumens appeared empty or contained scanty, lightly stained colloid. The acinar epithelium was from 8 to 10 microns high. The blood vessels were filled with blood cells. The glands resembled grossly and microscopically those observed in my former experiments with calcium chloride. The 30 animals of the second series, which had received the same calcium-rich diet but in addition had been given ten times the physiologic requirement of iodine, had slightly smaller thyroids than had the first group. The enlarged glands were light

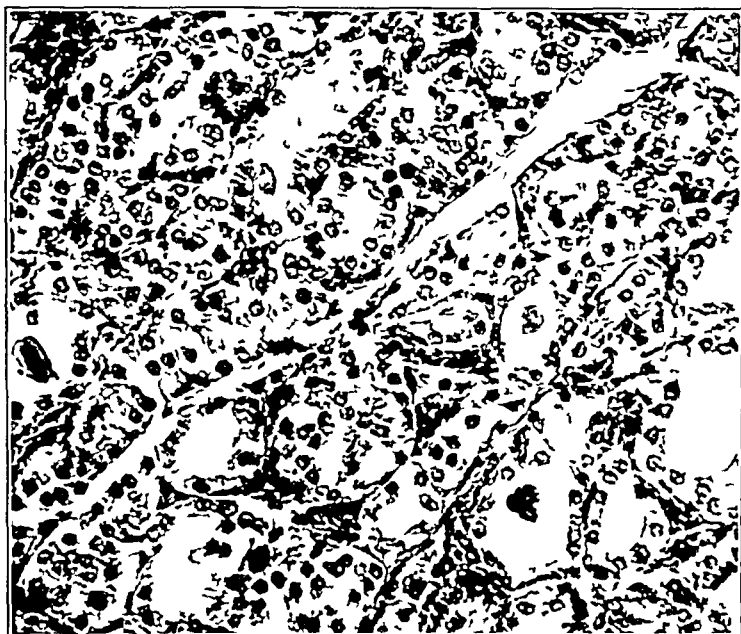


Fig 1—Diffuse parenchymatous goiter produced in a white rat by a diet high in calcium and low in iodine

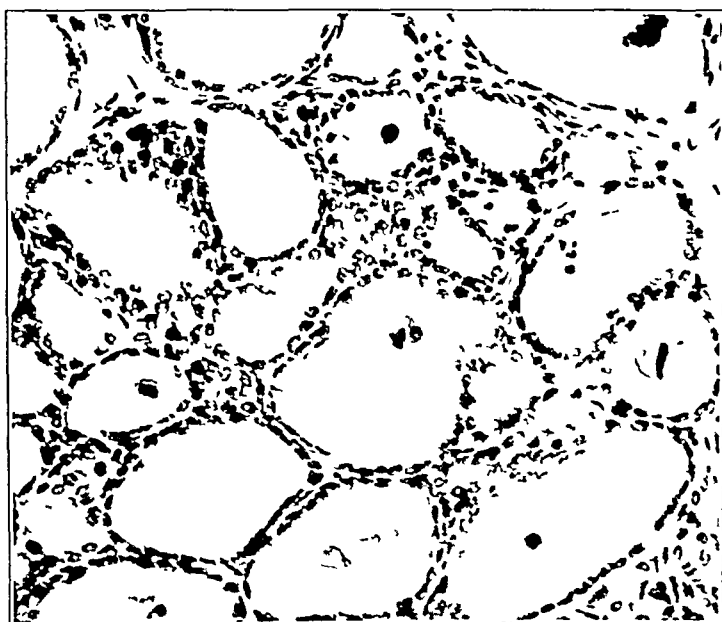


Fig 2—Diffuse colloid goiter produced in a white rat by a diet high in calcium and ten times the normal requirement of iodine

brown The diameter of the central acini varied between 80 and 120 microns Many wide acini were observed throughout the gland Solid or tubular acini were almost completely absent The colloid was well stained with eosin The height of the acinar epithelium was between 4 and 6 microns Sections of these thyroids showed colloid goiter with mild epithelial proliferation

COMMENT

The recent experiments have thus shown that goiter can be produced with regularity in white rats by a diet consisting of corn meal, rolled oats and calcium carbonate The goitrogenic factor in this diet is the calcium ion Secondary atrophy of the thyroid was not observed in spite of the fact that the experimental period was extended to eight months The addition of vitamins in the form of tomato juice did not interfere with the goitrogenic action of the calcium

The structure of the experimental goiters varied according to the iodine content of the goitrogenic diet A diet rich in calcium and low in iodine produced parenchymatous goiter, a diet rich in calcium and relatively rich in iodine produced colloid goiter The results of my experiments explain the fact that in regions where the iodine content of the food is sufficient for a normal intake, goiter will develop if a powerful positive goitrogenic factor is present Under these conditions, which are found in level regions (North America, northern Europe), the resulting goiter will be a colloid goiter The theory of iodine deficiency will never explain the development of colloid goiter¹¹

The results of these experiments are not only of theoretic interest but of great practical value from the standpoint of prophylaxis The daily intake of iodine required to prevent goiter is apparently not a constant It varies, depending on the presence and intensity of the positive goitrogenic factor

CONCLUSIONS

1 Calcium carbonate is as effective in producing goiter in white rats as is calcium chloride

2 Addition of vitamins to the goitrogenic diet does not prevent hyperplasia of the thyroid

3 Prolonged feeding of the goitrogenic diet does not produce secondary atrophy of the thyroid

4 Addition of ten times the normal requirement of iodine to the goitrogenic diet produces colloid goiter

5 Positive goitrogenic factors must be considered in the etiology of goiter

6 The amount of iodine required to prevent goiter is variable and depends on the presence and intensity of positive goitrogenic agents

11 Hellwig, C. A. The Diffuse Colloid Goiter, *West J Surg* 47:406, 1939

ETIOLOGY OF STONE IN THE COMMON BILE DUCT

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An increasing interest in functional disturbances which may be the underlying cause of pathologic changes in the common bile duct is manifest in the recent literature. Improvement of the technic of cholangiography for the study of dysfunction and pathologic conditions of the common duct has been the means of increasing knowledge of functional disturbances that seem to terminate in organic disease. This knowledge, as well as that derived from careful follow-up studies of cholecystectomized patients, has led to more frequent exploration of the common duct in recent years and, therefore, to an apparent increase in the incidence of stone in the common duct (Clute,¹ Lahey,² Cheever,³ Cattell,⁴ and others).

Kehr,⁵ Deaver,⁶ Moynihan,⁷ Lahey,⁸ Hermanson and Goldowsky,⁹ and Maingot¹⁰ are among the many authors who have emphasized the

From the Clinic for the Study of Disease of the Biliary Tract, New York Post-Graduate Medical School and Hospital

1 Clute, H M Common Duct Stones, J A M A **95** 1568 (Nov 22) 1930

2 Lahey, F H Common and Hepatic Duct Stones, New England J Med **207** 685, 1932 Lahey, F H, and Swinton, N W Stones in the Common and Hepatic Bile Ducts, *ibid* **213** 1275, 1935 Lahey, F H Earlier Operations in Cholelithiasis, S Clin North America **17** 725, 1937

3 Cheever, D Methods and Results in the Surgical Treatment of Diseases of the Biliary Passages, New England J Med **213** 463, 1935

4 Cattell, R B The Technique of Cholecystectomy and Cholecystostomy S Clin North America **17** 731, 1937

5 Kehr, H Wann soll man nach einer Ektomie bei negativem Palpationbefund von Steinen im Choledochus diesen Gang incidieren und drainieren und wann nicht? Arch f klin Chir **97** 301, 1912

6 Deaver, J B Surgery of the Common Bile Duct M Rec **80** 909 1911

(Footnotes continued on next page)

frequent neglect or oversight of lesions of the common bile duct, especially calculi. Young¹¹ observed that stones were still present at autopsy in the common bile ducts of 61 per cent of 67 patients who died of complications following cholecystectomy. Heyd and one of us (R. H.)¹² have shown in a previous publication that the incidence and severity of pathologic change in the common bile duct are directly proportional to the duration and severity of the preexisting disease of the gallbladder.

That this trend toward earlier surgical intervention in disease of the gallbladder has not prevented the secondary formation of calculi of the common duct has particularly stimulated the study of those factors which may be the cause of the formation of such stones in an attempt to prevent their occurrence.

It is our purpose to review briefly the literature on the normal and abnormal function of the common bile duct and to present our clinical pathologic studies of patients with disease of the common duct.

NORMAL PHYSIOLOGY OF THE COMMON DUCT

The function of the common duct is that of a conduit between the hepatic and cystic ducts and the duodenum. Its major structure is the sphincter of Oddi, found by Westphal¹³ to consist of a proximal muscular sleeve and a distal group of muscle fibers surrounding the ampulla of Vater. Normally the opening is only 1 to 2 mm in diameter.¹⁴ This mechanism controls the flow of the bile into the duodenum, normally an intermittent function dependent on a number of stimuli (Rost,¹⁵

7 Moynihan, B. Secondary Operations on the Biliary System, *Lancet* **2** 4, 1923.

8 Lahey, F. H. The Incidence and Management of Stones in the Common and Hepatic Ducts, *Tr. Am. S. A.* **51** 164, 1933.

9 Hermanson, L., and Goldowsky, S. Occurrence of Common Duct Stone Following Gallbladder Operations, *New England J. Med.* **211** 806, 1934.

10 Maingot, R. Biliary Tract Surgery, *Post-Grad. M. J.* **13** 213, 1937.

11 Young, E. L. Possibilities of Failure in Removal of Stones in Biliary Tract, *New England J. Med.* **200** 1145, 1929.

12 Heyd, C. G., and Hotz, R. Surgery of the Common Duct, *Am. J. Surg.* **44** 677, 1939.

13 Westphal, K. Die Bewegungs- und Resorptionsstörungen an den Gallenwegen und ihre Gefahren, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 1932, Kong. **44**, p. 354.

14 Weiss, S. Diseases of the Liver, Gallbladder, Ducts and Pancreas, New York, Paul B. Hoeber, Inc., 1935.

15 Rost, F. Die funktionelle Bedeutung der Gallenblase. Experimentelle und anatomische Untersuchungen nach Cholezystektomie, *Mitt. d. Grenzgeb. d. Med. u. Chir.* **26** 710, 1913.

Mann,¹⁶ Mann and Bollman,¹⁷ and others) Rost observed that after extirpation of the gallbladder in dogs a continuous trickle of bile flowed from the ampulla and so contributed experimental evidence of a reciprocal contrary innervation between the gallbladder and the sphincter of Oddi. Such an innervation hypothecates that during the resting phase of activity of the gallbladder the organ is relaxed and allowed to fill by the tonicity of the sphincter of Oddi, whereas certain stimuli, notably food and hydrochloric acid in the duodenum, cause the sphincter to relax and the gallbladder to contract. Mentzer,¹⁸ Berg,¹⁹ Berg and Jobling,²⁰ McMaster and Elman,²¹ Whitaker,²² Ravdin and Johnston²³ and Boyden²⁴ have expressed a contrary opinion. Bollman and Mann concluded that the normal intermittent flow of bile from the ampulla of the dog is due to the action of the duodenal musculature. The entire problem of dyskinesia of the gallbladder, as presented by Ivy and Sandbloom,²⁵ and that of dyskinesia of the common duct, as elaborated by Best and Hicken,²⁶ is dependent on a disturbance of the probable reciprocal relation just described.

Contraction or spasm of the common duct elsewhere than at its terminal portion (sphincter of Oddi) is highly questionable in view of

16 Mann, F. C. A Study of the Tonicity of the Sphincter at the Duodenal End of the Common Duct, *J. Lab. & Clin. Med.* **2** 107, 1919, The Function of the Gallbladder, *Physiol. Rev.* **4** 251, 1924.

17 Mann, F. C., and Bollman, J. L. Jaundice. A Review of Some Experimental Investigations, *J. A. M. A.* **104** 371 (Feb. 2) 1935.

18 Mentzer, S. J. The Disturbances of the Law of Contrary Innervation as a Pathologic Factor in Diseases of the Bile Ducts and the Gallbladder, *Am. J. M. Sc.* **153** 469, 1917.

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20 Berg, B. N., and Jobling, J. W. The Effect of Division and Transplantation of the Common Duct upon the Gallbladder, *Proc. Soc. Exper. Biol. & Med.* **24** 434, 1927.

21 McMaster, P. D., and Elman, R. On the Expulsion of Bile by the Gallbladder and a Reciprocal Relationship with the Sphincteric Activity, *J. Exper. Med.* **44** 173, 1926.

22 Whitaker, L. R. The Mechanism of the Gallbladder and Its Relationship to Cholelithiasis, *J. A. M. A.* **88** 1542 (May 14) 1927.

23 Ravdin, I. S., and Johnston, C. G. The Gallbladder. Recent Advances as Applied to Treatment, *Pennsylvania M. J.* **35** 357, 1932.

24 Boyden, E. A. Sphincter of Oddi in Man and Certain Representative Mammals, *Surgery* **1** 25, 1937.

25 Ivy, A. C., and Sandbloom, P. Biliary Dyskinesia, *Ann. Int. Med.* **8** 115, 1934.

26 Best, R. R., and Hicken, N. F. Biliary Dysynergia, *Surg., Gynec. & Obst.* **61** 721, 1935.

the careful anatomic study made by MacDonald²⁷. He could demonstrate no circular muscle fibers and only occasional isolated longitudinal fibers in the wall of the common bile duct in man. Mirizzi,²⁸ however, claimed to have seen typical spastic defects in the common hepatic ducts of patients for whom cholangiographic study was made. He noted the disappearance of such defects in subsequent roentgenograms. Such defects have been attributed by other observers to the presence of mucus in the duct.

The mucous membrane of the common duct is irregular and broken by minute depressions which open or lead to two types of structures, small saclike appendages called parietal sacculi (Theile²⁹) and short blind ducts called vasa aberrantia (Holmes³⁰). Their function is not known, although Beale³¹ concluded that they are accessory gallbladders capable of taking over the function of the gallbladder when it is diseased. Ravdin and Johnston attributed a glandular activity to these structures. The mucous membrane of the common duct or its appendages does secrete a watery alkaline solution into the lumen of the common duct (Rous and McMaster³²), though the role and the volume of this diluting solution have not been determined.

PATHOLOGIC PHYSIOLOGY OF THE COMMON BILE DUCT

Studies on the common duct of animals, particularly dogs, and cholangiographic study of the common duct of the human being, as practiced by Mirizzi,³³ Saralegui,³⁴ Walters and Theeson,³⁵ Best and

27 MacDonald, I. S. Histology of the Biliary Ducts and Its Correlation with the Symptomatology of Common Duct Stone, *Surg, Gynec & Obst* **60** 775, 1935

28 Mirizzi, P. L. Operative Cholangiography. Contribution to Physiopathology of the Common Bile Duct, *Lancet* **2** 366, 1938

29 Theile, I. Die Leber, in Wagner, R. Handwörterbuch der Physiologie, Brunswick, F. Vieweg u. Sohn, 1842-1853, vol. 2, p. 349

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31 Beale, L. S. Lectures on the Principles and Practice of Medicine. The Liver, London, J. & A. Churchill, 1899

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33 Mirizzi, P. L. La colangiografía durante las operaciones de las vías biliares, *Bol y trab de la Soc de cir de Buenos Aires* **16** 1133, 1932, La cholangiographie durant l'operation (C. D. O.) Constatations et resultats de la seconde serie de cent opérations seniles voies biliaires, *Bull et mem Soc nat de chir* **61** 349, 1935, Die Anwendung der Cysticoduodenostomie, *Deutsche Ztschr f Chir* **246** 609, 1936, Operative Cholangiography, *Surg, Gynec & Obst* **65** 702, 1937

34 Saralegui, J. A. Cholangiography. New Technique and Results, *Am J Roentgenol* **32** 167, 1934, Die Cholangiographien beim Studium der Gallenleiden, *Fortschr a d Geb d Röntgenstrahlen* **52** 571, 1935

Hicken³⁶ and others, form the basis of such knowledge as physicians now possess of the abnormal function of the extrahepatic bile ducts. From such studies certain assumptions have been made possible, especially as to function of the common bile duct after cholecystectomy.

It is generally recognized that the common bile duct in man assumes some of the function originally resident in the gallbladder when the latter is extirpated by operation or by disease. Sweet,³⁷ in 1924, found the parietal sacculi of the hepatic ducts and of the common bile duct enlarged after cholecystectomy. From his chemical studies of the blood of cholecystectomized dogs he made the deduction that the parietal sacculi assume the function of the gallbladder, particularly in regard to absorption of cholesterol. Boyd³⁸ stated a similar opinion. An enlargement of the vasa aberrantia has also been described by Boyd,³⁸ Sweet,³⁷ Sutton³⁹ and Schmidt and Ivy.⁴⁰ Counseller⁴¹ did not find these changes except when the common duct itself is dilated. This dilatation is common after partial intermittent obstruction and after cholecystectomy, as has been pointed out by Judd and Mann.⁴² Cox,⁴³ in a study of autopsy specimens from cholecystectomized patients, concluded that the dilatation of the accessory structures is merely concomitant with dilatation of the common duct and is not a specific response to cholecystectomy. He was able to demonstrate no epithelial hypertrophy or secretory glands before or after obstruction of the common duct or cholecystectomy and therefore concluded that the appendages have no specific function. That the

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36 Best, R. R., and Hicken, N. F. Cholangiographic Demonstration of Biliary Dyssynergia and Other Obstructive Lesions of the Gallbladder and Bile Ducts, *J. A. M. A.* **107** 1615 (Nov. 14) 1936, Biliary Dyssynergia. Cholangiographic Recognition and Its Significance, *West. J. Surg.* **44** 467, 1936, Technique of Immediate Cholangiography, *Surg., Gynec. & Obst.* **65** 217, 1937.

37 Sweet, J. E. The Gallbladder. Its Past, Present, and Future, *Internat. Clin.* **1** 187, 1924.

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42 Judd, E. S., and Mann, F. C. The Effect of the Removal of the Gallbladder. An Experimental Study, *Surg., Gynec. & Obst.* **24** 437, 1917. Mann, F. C. A Physiologic Consideration of the Gallbladder, *J. A. M. A.* **83** 829 (Sept. 13) 1924.

43 Cox, F. M. Changes in the Bile Ducts and Parietal Sacculi Following Absence of the Gallbladder, *Surg., Gynec. & Obst.* **55** 169, 1932.

dilatation observed after cholecystectomy is dependent on the function of the sphincter of Oddi has been demonstrated by Judd and Mann,⁴² Doubilet and Colp⁴⁴ and Winkelstein and Aschner.⁴⁵ They were unable to secure dilatation of the common duct if the sphincter had been destroyed or the ampulla cannulized.

In 1903, Krukenberg reported a case of gallbladder colic without gallstones. Since that time, not only colic but dilatation of the gallbladder and the common duct without stones or evident obstruction has been increasingly recognized and attributed to a neurogenic mechanism which increases the tone of the sphincter of Oddi (Best and Hicken,³⁶ Ivy and Sandbloom,²⁷ Berg,¹⁹ Walters, McGowan, Butsch and Knepper,¹⁶ and others). Ivy,⁴⁷ Potter and Mann⁴⁸ and Doubilet and Colp⁴⁴ have found pressures up to 400 mm of water necessary to overcome the resistance of spastic sphincters. Best and Hicken³⁶ and others have shown such an increased tone to be the cause for dilatation of the common duct, a view contrary to the results of experimental studies of Puestow.⁴⁹ They concluded that such a spastic dysfunction causes stagnation of bile and is the precursor of infection and calculi, a view also held in part by Beer,⁵⁰ Walters⁵¹ and Beall⁵² for intrahepatic stones.

The recurrent stones found in some common ducts after cholecystectomy and prolonged drainage of the common duct when no organic obstruction is demonstrable can probably best be explained on the basis of continuing spasm and infection. Puestow,⁴⁹ in a study of 85 cholecystectomized patients, found a total lack of tone in the sphincter in the majority of instances and concluded that the dilatation of the common duct is passive or atonic. This contention is difficult to appraise, in view

44 Doubilet, H, and Colp, R. Resistance of the Sphincter of Oddi in the Human, *Surg, Gynec & Obst* **64** 622, 1937, Endocholedochal Sphincterotomy, *ibid* **66** 882, 1938.

45 Winkelstein, H, and Aschner, P. W. The Mechanism of the Flow of Bile from the Liver into the Intestines, *Am J M Sc* **171** 104, 1926.

46 Walters, W, McGowan, J. M., Butsch, W. L., and Knepper, P. A. Pathologic Physiology of the Common Bile Duct. Its Relation to Biliary Colic, *J A M A* **109** 1591 (Nov 13) 1937.

47 Ivy, A. C. Physiology of the Gallbladder, *Physiol Rev* **14** 1, 1934.

48 Potter, J. C., and Mann, F. C. Pressure Changes in the Biliary Tract, *Am J M Sc* **171** 202, 1926.

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50 Beer, E. Intrahepatic Cholelithiasis, *M News* **85** 202, 1904.

51 Walters, W. The Pathologic Physiology of Stone in the Common Bile Duct, *Surg, Gynec & Obst* **63** 417, 1936.

52 Beall, F. C. Stones in the Common Bile Duct, *Ann Surg* **107** 238, 1938.

of the clinical and experimental data which contradict it Newman⁵³ has noted temporary atony of the sphincter following cholecystectomy, but the tone rapidly returned to normal or increased levels, a cycle we have noted cholangiographically in our own studies

It is probable that the course of events in the formation of recurrent calculi of the common duct without organic obstruction is that of increased spasm of the sphincter causing backing or stagnation of bile with oversaturation and therefore precipitation of cholesterol and calcium salts. Continued stagnation and precipitation tend toward the formation of stones, which, as in the gallbladder, predispose to irritation of the mucous membrane and infection. Whether infection of the common duct precedes or follows the formation of stone is debatable and of little consequence in this discussion. That the two are frequently coexistent has been demonstrated by many observers cited previously in this section.

RESULTS OF STUDY ON DISEASE OF THE COMMON DUCT

During the past seven years, 239 operations were performed on the gallbladders and bile ducts of patients who had been studied in the "gallbladder clinic" of the New York Post-Graduate Medical School and Hospital. In 47 instances, or 20 per cent, exploration of the common duct was performed. As in other clinics, the frequency of exploration of the common duct in this institution has increased during the past few years, in 30 per cent of the last 100 cases of this series such an exploration was done. Stones were present in 21 cases, in all of the remainder there was dilatation of the common bile duct due either to spasm of the sphincter or to some obstruction other than stone. A comparison between these two groups of cases, i.e., those in which stones were present and those in which they were absent, has been undertaken with the hope of determining the etiology of the common duct stones encountered.

The study consisted of routine preoperative cholecystographic examination, duodenal drainage, chemical study of the blood, chemical and bacteriologic examination of bile and stones from the gallbladder and from the common duct, the taking of a postoperative cholangiogram in 8 cases and daily chemical studies of bile from the common duct up to the time the drainage tube was removed from the duct.

Preoperative (Diagnostic) Findings—The average age of the 21 patients with common duct stone was 60 years, in contrast to an average age of 45 years for patients with dilated common ducts in which no stones were found. Similarly, the duration of symptoms suggestive of disease of the biliary tract was longer in the cases in which stones were

53 Newman, C. Physiology of the Gallbladder and Its Functional Abnormalities, *Lancet* 1 785, 841 and 896, 1933

present Biliary colic was a major complaint of 18, or 86 per cent, of patients with common duct stones but had only a 50 per cent incidence in patients with dilatation of the common duct without stones. A history of jaundice was twice as frequent for the patients with common duct calculi as for those without (70 per cent versus 31 per cent) but was sometimes not given for patients with markedly dilated common ducts containing multiple calculi. Dyspepsia was a complaint of all the patients in this series.

Studies of the blood were of little value in differentiating between the patients with stone and those without. A mild elevation of the leukocyte count was frequently associated with the presence of common duct stones but was seldom observed in the absence of stone unless pancreatitis was present. In patients with an elevated icterus index and a positive van den Bergh reaction the value for blood cholesterol was usually elevated above 220 mg per hundred cubic centimeters. This was seen more frequently in patients with calculous common ducts, for, generally speaking, the icterus index when elevated in cases of calculus was higher than in cases in which calculi were absent. The incidence of an elevated icterus index was higher (81 per cent versus 50 per cent) in the patients with stones in the common duct than in those without.

Duodenal drainage furnished significant diagnostic data. Concentrated bile and clumped crystals of calcium bilirubinate (bile sand) were frequent in patients with common duct stone, whereas a combination of these was seldom found in patients without stones. Chemical determinations of the level of cholesterol in the duodenal bile were not of importance. Usually only a trace (50 mg per hundred cubic centimeters) of cholesterol was present. Of the greatest differential value was the finding on sterile drainage by the encapsulated method (Twiss⁵⁴) of colon bacilli or streptococci in the drainage. These organisms, singly or together, were present in more than 80 per cent of patients with common duct stones, as against a 34 per cent incidence in patients without stone. Furthermore, cultures yielding these organisms were generally associated with the "bile sand" in patients with stone. Pure cultures obtained from duodenal specimens (only one organism) were common in patients with stone and much less common in those without.

The results of examination of the gastric contents for hydrochloric acid were significant only in that hypochlorhydria was found in all patients with common duct stone, as against a less frequent occurrence in patients without stone.

54 Twiss, J R. Technic of Non-Surgical Drainage of the Biliary Tract, *J A M A* **100** 792 (March 17) 1933. Twiss, J R, and Phillips, C H. Bacteriological Findings in Disease of the Biliary Tract. An Improved Method of Obtaining Cultures of Bile by Duodenal Drainage, *Am J Digest Dis & Nutrition* **2** 663, 1936.

A cholecystogram was taken in the clinic in 23 cases. In no instance was a normally visualizing gallbladder found. Twenty films showed no visualization, and 3 had a faint visualization. The value of the cholecystogram in determining the function of a gallbladder cannot be overestimated, as we have found a 90 per cent agreement between the cholecystogram and the pathologic findings in the cases of over 200 cholecystectomized patients.

Table 1 is a resume of the preoperative findings in cases of disease of the common duct with and without stones. This study gives presumptive evidence that dilatation of the common duct is often dependent on loss of function of the gallbladder (roentgen evidence) and that

TABLE 1—*Resume of Diagnostic Findings in Cases of Disease of the Common Duct With and Without Stone*

Diagnostic factors	Calculous Common Duct (21 Cases)	Dilated Noncalculous Common Duct (26 Cases)
Age of patients	50 to 70 years	35 to 50 years
Mean age of patients	60 years	44 years
Total duration of symptoms referable to gallbladder	10 to 40 years	2 to 20 years
Incidence of biliary colic	86%	54%
Incidence of jaundice (by history)	70%	38%
Leukocyte count	Slightly elevated (10,000-14,000)	Normal except with pancreatitis
Icterus index	9+ units in 90%	9+ units in 65%
Duodenal drainage		
Concentrated bile	In duodenum, 65%	In duodenum, 35%
Crystals	Clumped calcium bilirubinate and calcium	Cholesterol crystals
Culture of duodenal contents	Colon bacilli or streptococci in 80%	Mixed or sterile cultures in 70%
Gastric acidity (free)	Achylia or hypochlorhydria in all but 1 case	Various
Cholecystogram	Visualization in only 1 case	Visualization in only 2 cases

this is associated with intermittent spasm of the sphincter of Oddi. The frequent finding of concentrated bile and crystals in drainage of the common bile ducts of patients with nonfunctioning gallbladders is further evidence that the common bile duct may take over some of the concentrating function of the gallbladder and that stasis of bile in the common duct may occur.

The advanced age of the patients, the high incidence of cultures yielding bacteria and the associated hypochlorhydria observed in cases of common duct stone are indicative that prolonged stasis predisposes to stone formation and infection, much as the same train of events previously occurred in the gallbladder. There is no invariable or pathognomonic finding in cases of common duct stone. The history of jaundice, colic and prolonged digestive symptoms in patients in the fifth to the seventh decade of life, a nonfunctioning gallbladder on roentgen examina-

tion and the finding of clumped calcium or calcium bilirubinate crystals associated with colon bacilli or a streptococci are highly presumptive evidence of stone in the common duct

Findings at Operation—At operation chemical, bacteriologic and pathologic studies were made of the gallbladder and of bile from the common duct Table 2 is a resume of the pathologic changes in the gallbladder as determined by the attending pathologist and of the appearance of the common duct as described by the operating surgeon The pathologic changes in the gallbladder were in close accord with the results of preoperative cholecystographic examination Pathologic changes were far advanced in all but 2 cases, and stones were present in the gallbladder in 35 of the 37 specimens

TABLE 2—*Macroscopic and Microscopic Pathologic Changes Found at Operation in Patients with Disease of the Common Duct*

	Calculous Common Duct	Noncalculous Common Duct
Disease of gallbladder (attending pathologist's report)		
Chronic cholecystitis and lithiasis	2	7
Severe (ulcerative) cholecystitis with lithiasis	10	8
Acute cholecystitis and lithiasis	1	7
Chronic noncalculous cholecystitis	1	1
No gallbladder (cholecystectomy)	7	3
Total number of cases	21	26
Disease of common duct (operating surgeon's report)		
Dilatation with acute pancreatitis		3
Dilatation with chronic pancreatitis		6
Dilatation (no other pathologic change noted)	19*	16
Dilatation with acute cholangitis	2	
Operative injury, stenosis		1
Total number of cases	21	26

* In 1 of these cases there was generalized papillomatosis at the lower end of the common duct

In 16 instances no cause for the dilatation of the common duct could be ascertained The appearance of the duct and the degree of associated disease of the gallbladder were the same as those present in the 18 cases of common duct stone in which no other cause for obstruction was observable The only difference indicated in this group by contrasting findings was that the incidence of cultures yielding bacteria was much lower in the cases in which stones were absent and the duration of disease of the biliary tract, as reflected in symptoms, was much shorter It was in these conditions (noncalculous) that hypertonicity of the sphincter of Oddi (sphincter spasm) without benefit of the regulatory function of a gallbladder offered the most likely explanation for the dilatation

Pancreatitis, either acute or chronic, was a probable obstructing factor in 9 patients without stones of the common bile duct In no case

of common duct stone was pancreatitis deemed present, a finding contrary to that frequently reported in the literature. Stones were frequently found in common ducts which were dilated after a previous cholecystectomy. From this limited series no conclusion can be drawn concerning the incidence of postoperative common duct stones, for exploration of the duct was done only in cases of intermittent jaundice, bile sand and cultures yielding bacteria.

The microscopic, chemical and bacteriologic data on the bile and on the stones from the gallbladders of patients with disease of the common duct are given in table 3. They serve to substantiate the pathologist's report and to add further evidence of the fact that disease of the common duct is a sequel of severe disease of the gallbladder. The findings indicate that the pathologic process in the gallbladder was farther advanced in the patients with common duct stones than in those without.

TABLE 3—*Chemical, Microscopic and Bacteriologic Findings in the Bile of Gallbladders of Patients with Disease of the Common Duct*

	Calculous Common Duct (14 Cases)	Noncalculous Common Duct (23 Cases)
Bile salts (average)	280 mg /100 cc	2 000 mg /100 cc
Cholesterol (average)	211 mg /100 cc	362 mg /100 cc
Incidence of crystals	100%	100%
Calcium bilirubinate	7 cases	7 cases
Calcium	6 cases	1 case
Cholesterol	6 cases	9 cases
Incidence of pancreatic ferments	50%	45%
Incidence of cultures yielding bacteria	64%	53%

In all the cases in this series the common duct was dilated at the time of operation. The degree of dilatation was no greater in patients with stone than in patients without stone. It was impossible to determine the original source of the common duct stones, i. e., whether it was the gallbladder, the common bile duct or the hepatic ducts. In only 3 cases were there stones in the common bile duct with the appearance and structure of ordinary "mixed" gallstones. In 16 the stones were composed predominantly of calcium bilirubinate, and in 2 they were pure pigment stones. It is probable that both the calcium bilirubinate stones and the pigment stones were formed in the common duct, as they were in marked contrast chemically and structurally to their associates in the gallbladder.

Bile from the common duct, procured at the time of operation, was examined chemically, microscopically and bacteriologically. The results of the examinations are given in table 4. The patients were, as in the previous studies, divided into those with stone and those without. The results revealed no evidence not previously shown by duodenal drainage.

Common ducts which contained stones showed concentrated bile and concentrated cholesterol more frequently than did ducts without stones. As the patients had nonfunctioning gallbladders in every instance in which the common duct bile was observed before operation to be concentrated, there is little question of the transference of this function to the common duct once the gallbladder is removed by a pathologic process. The ability to concentrate bile was not general in calculous common ducts. Common ducts in which the calculus had produced a long-standing, nearly complete obstruction had a low concentration of bile salts and cholesterol, just as is seen in cases of obstruction (hydrops) of the

TABLE 4—*Chemical, Microscopic and Bacteriologic Findings in Bile Obtained from the Common Duct at Operation*

	Calculous Common Duct (21 Cases)	Noncalculous Common Duct (26 Cases)
Concentrated bile (800 mg /100 cc + bile salts)	53%	27%
Bile cholesterol		
50 mg /100 cc or more	6 cases	4 cases
Less than 50 mg /100 cc	12 cases	12 cases
Crystals	90%	53%
Calcium bilirubinate	17 cases	9 cases
Calcium	2 cases	1 case
Cholesterol	4 cases	11 cases
None	2 cases	2 cases
Pancreatic ferments		
Present	11 cases	5 cases
Absent	7 cases	7 cases
Cultures	90% positive	53% positive
Colon bacilli	13 cases	5 cases
Streptococci	8 cases	3 cases
Mixed (2 or more organisms)	7 cases	0 case
Sterile	2 cases	10 cases
Other organisms	3 cases	3 cases

gallbladder. When these findings for the operative bile specimens (not concentrated) are correlated with those obtained by postoperative T-tube drainage, it is evident that the role of the liver cannot be overlooked, i. e., in cases of severe obstruction, the liver did not secrete normal bile. The finding of "white" bile (bile containing no cholesterol or bile salts) is evidence that under severe abnormal conditions the common duct may absorb bile salts, pigment and cholesterol.

Pancreatic ferments were more frequently present in the bile of common ducts containing calculi than in that of noncalculous ducts. This could not have been due to the impaction of a stone in the ampulla except in 3 instances. It is apparent that a certain degree of sphincter tone, probably greater than is physiologic, existed, either because of the stones or independently of them. Microscopic examination confirmed

the finding by duodenal drainage of calcium bilirubinate crystals in calculous common ducts and of a variety of crystals in noncalculous ducts. A marked degree of stasis was evident in all of the common ducts exposed.

Cultures of the operative specimens of bile from the common ducts revealed viable organisms in all but 2 calculous common ducts, with colon bacilli and/or streptococci in 75 per cent of all ducts. Only 33 per cent of noncalculous common ducts contained these organisms.

A daily analysis of the bile obtained by T-tube drainage was made in each case. The values for bile salts, cholesterol and ferment concentration were determined, and crystals were noted. In reviewing the results of this extensive chemical study, no evidence as to the functional state of the common duct was obtained except that the bile procured by "free" drainage of the tube was lower in concentration than was that procured after a period of obstruction (clamping) of the tube. As the period of drainage extended and presumably edema and spasm subsided, these variations became less marked, until, apparently with free drainage into the duodenum, no change in concentration existed. The concentration of bile salts from the fistulas of patients with long-continued partial obstruction was generally low. This was true of patients without evident hepatic damage. It is evident that the liver was secreting bile low in bile salt and cholesterol. Such variables as this, as well as spasm or atony of the sphincter, make a specific chemical study of post-operative common duct bile of little value in determining the functional status of the common duct.

A postoperative ("delayed") cholangiogram was taken in 8 cases. In only 1 instance was there evidence of continuing organic obstruction, the patient had papillomatosis of the lower end of the common duct. Five of the patients, however, revealed a functional spasm of the sphincter of Oddi, proved by retention of dye in the common duct with prompt emptying on inhalation of amyl nitrite. This finding of spasm even in such a small series of cases lends support to the theory that the cycle of events we have recorded in our studies may be initiated by spasm of the sphincter and that removal of the results of dysfunction (cholelithiasis, chronic cholecystitis or choledocholithiasis) does not necessarily relieve the patient of the consequences of continuing dysfunction.

The difficulties inherent in a study of the physiology and of the abnormal functions of the common bile duct in cholecystectomized patients are best illustrated by the 2 case histories which follow.

REPORT OF CASES

CASE 1—R. W., a white woman aged 50, was admitted to the hospital with a history of epigastric distress, nausea and vomiting for twenty years. During the five years prior to her admission she had definite episodes of epigastric colic

radiating to the lower angle of the right scapula. On examination she had deep epigastric tenderness.

Laboratory examination showed normal values for blood cholesterol and cholesterol esters. The icterus index was 9. The van den Bergh reaction was negative. The duodenal contents yielded a pure culture of *Bacillus coli*. The gallbladder did not visualize roentgenographically. Shadows were seen which were interpreted as representing calculi of the gallbladder.

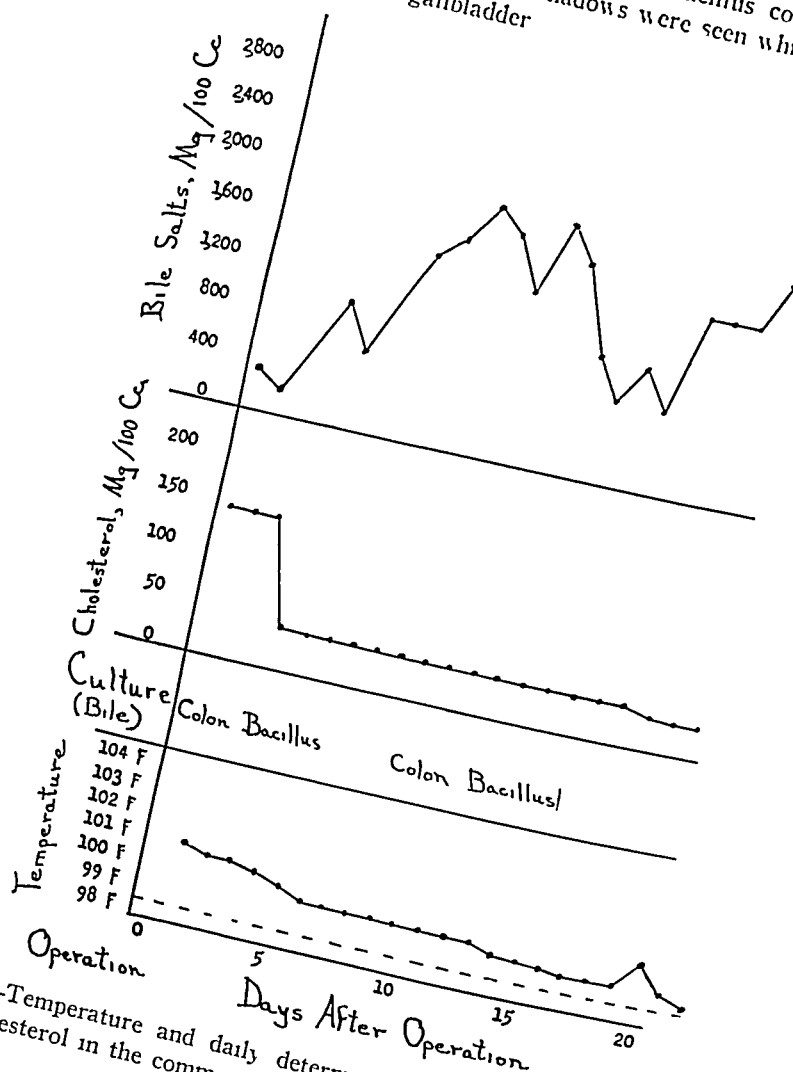


Chart 1—Temperature and daily determinations of the concentration of bile salts and cholesterol in the common bile duct in case 1

At operation the gallbladder proved to be functionless (hydrops) and filled with mixed gallstones. The common bile duct was dilated and contained several large calcium bilirubinate stones different in structure and composition from those found in the gallbladder. Cholecystectomy and choledochostomy were performed. On analysis the bile obtained from the common duct at operation was dilute, containing 310 mg of bile salts and 50 mg of cholesterol per hundred cubic centimeters. It contained also clumped calcium bilirubinate crystals, pancreatic ferments of normal activity and colon bacilli.

Comment—Daily determinations of the composition of the “fistula bile” are recorded in chart 1. The gradual rise in concentration of the bile salts is attributable to an increasing recovery of hepatic function and also in part to the ability of the common bile duct to concentrate bile. The cholesterol content remained relatively constant. Pancreatic ferments and crystals were present in the bile throughout the period of drainage.

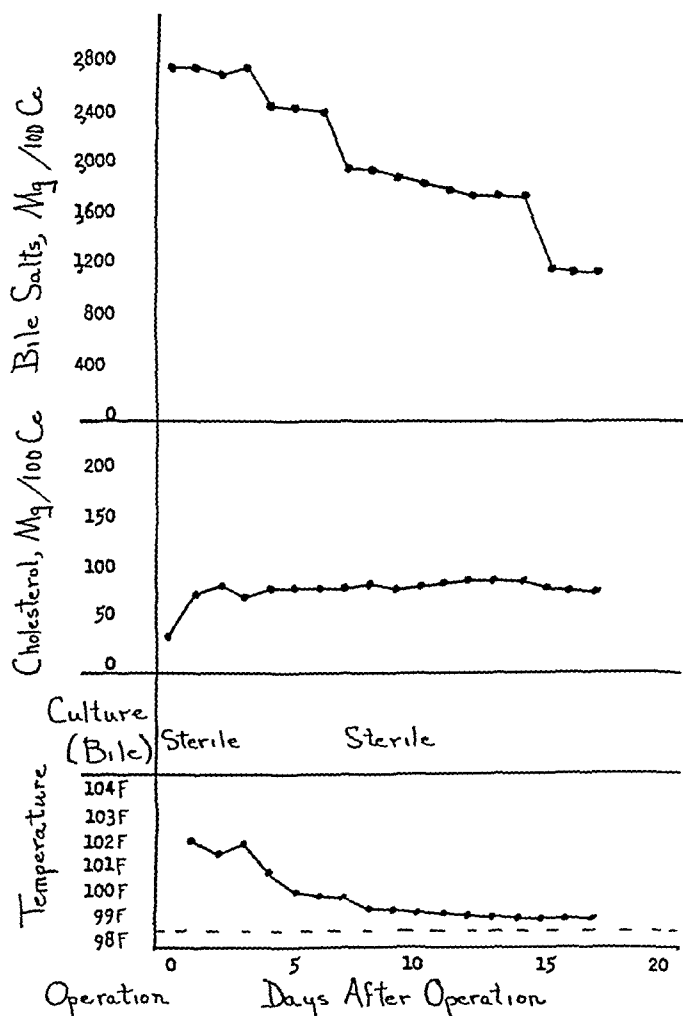


Chart 2—Temperature and daily determinations of the concentration of bile salts and cholesterol in the common bile duct in case 2

Cultures of the bile obtained by drainage ten days after the operation showed the continued presence of the colon bacillus infection. A cholangiogram taken on the sixteenth postoperative day showed a normally functioning sphincter of Oddi.

Repeated postoperative studies of material obtained by duodenal drainage have shown a continuing colon bacillus infection of the com-

mon bile duct with alternate dilute and concentrated bile. The patient has been free from symptoms except for rare episodes of mild indigestion. The threat of a recurrent common duct stone is present, and stones may recur if the stasis in the common bile duct is not controlled.

CASE 2—A white man aged 50 was admitted to the hospital with a history of severe intermittent epigastric pain radiating to the right upper quadrant of the abdomen for five months. He had had jaundice, chills, nausea and vomiting. On examination he showed jaundice, tenderness in the right upper abdominal quadrant and in the epigastrium, a mass in the right hypochondrium and evidence of loss of weight.

Laboratory examination showed the value for blood cholesterol to be 290 mg and that for cholesterol esters 122 mg per hundred cubic centimeters. The icterus index was 18.3. The van den Bergh reaction was direct. Duodenal drainage showed concentrated bile, many cholesterol crystals and occasional calcium bilirubinate crystals. A culture of the duodenal contents was sterile. The gallbladder did not visualize roentgenographically.

At operation the gallbladder was totally obliterated, filled with tightly packed "mixed" gallstones. The common bile duct was dilated but contained no stones. The pancreas was normal. Cholecystectomy and choledochostomy were performed. The bile obtained from the common duct was concentrated, containing 2,700 mg of bile salts and 25 mg of cholesterol per hundred cubic centimeters. It contained also numerous cholesterol crystals and some calcium bilirubinate crystals. Culture of material from the common bile duct was sterile.

Comment—Daily determinations of the composition of the "fistula bile" are recorded in chart 2. As the edema in the duct subsided, the concentration of bile salts returned to normal and the stasis, as shown by the crystalline sediment, decreased. The cholesterol content remained at 80 to 100 mg per hundred cubic centimeters, apparently the concentration being secreted by the liver. Additional cultures of the bile obtained by drainage were sterile. A cholangiogram taken on the nineteenth postoperative day showed a normal sphincter of Oddi, with perhaps a slightly increased tone as shown by a visualization of the pancreatic duct. The dye, however, emptied readily from the duct.

In this patient the disease was of short duration and the dysfunction, dilatation and stasis of the common bile duct followed rapidly on obstruction of the cystic duct and obliteration of the gallbladder. It is probable that had dysfunction of the common bile duct continued for a longer period stone formation and infection would have taken place.

SUMMARY AND CONCLUSIONS

A comparison is made between a series of cases of stone of the common duct and a series of cases of disease of the common duct without stone.

In the majority of cases the common duct stones were not related structurally to the gallbladder stones, and therefore a different cause

must be assumed. In most instances the disease originates in the gallbladder, and with the passage of time the gallbladder becomes obliterated and functionless while the common duct to a greater or lesser degree takes over the concentrating ability of the gallbladder. This is evidenced by the increased concentration of the bile in the common ducts of patients with advanced cholecystic disease.

This concentration of bile is further increased by stasis, which in the presence of gastric achylia predisposes to infection. This combination of factors favors the deposition of bile sand and the formation of calcium bilirubinate stones. As such, common duct stone represents a separate pathologic entity distinct from, though related to and dependent on, the preexisting chronic cholecystitis. The failure of cholecystectomy to break this chain of events probably explains recurrent, as contrasted to overlooked, stones of the common duct.

LYMPHOSARCOMA OF THE STOMACH

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The proper classification of tumors arising in lymphoid tissue presents great difficulties. The reports on this subject by Foot,¹ Connor,² Oberling³ and others all show a divergence of opinion and nomenclature. To avoid confusion, then, we shall use in this discussion the classification of sarcomas of the gastrointestinal tract employed by Ewing,⁴ namely (1) spindle cell myosarcoma, (2) miscellaneous round cell or mixed cell alveolar sarcoma and (3) lymphosarcoma.

The spindle cell myosarcoma is likely to be bulky, cystic or solid, it may project into the peritoneal cavity or into the lumen of the stomach, it is noninfiltrating and is late in metastasizing.

Tumors of the miscellaneous round cell type constitute a group about which little is known and for this reason probably do not deserve being classified as a separate variety.

Lymphosarcomas constitute the largest and most important group, of which there are two varieties, differing in the type of cell from which the tumors arise: the reticulum cell sarcoma, arising from the reticulum cells of the germ centers of the follicles and pulp cords, and the malignant lymphocytoma, or small round cell lymphosarcoma, arising from the lymphocytes.

The embryologic origin of the reticulum cell is unknown, but it is certain that neoplastic growths of lymphoid tissue may appear in the

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Abridgment of a thesis submitted by Dr Madding to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirement for the degree of Master of Science in Surgery.

1 Foot, N C. Report of a Case of Malignant Endothelioma with Necrosis, *J M Research* **44** 417-430, 1924.

2 Connor, C L. Endothelial Myeloma, Ewing. Report of Fifty-Four Cases, *Arch Surg* **12** 789-829 (April) 1926.

3 Oberling, C. Les reticulosarcomes et les réticulo-endothéliosarcomes de la moelle osseuse (sarcomes d'Ewing), *Bull Assoc franç p l'étude du cancer* **17** 259-296 (May) 1928.

4 Ewing, J. Neoplastic Diseases, ed 3, Philadelphia, W B Saunders Company, 1928.

stomach and by invasion destroy it Roulet⁵ expressed the opinion that lymph nodes possess two types of stroma one consisting of fibrous connective tissue, from which the true fibrosarcoma or spindle cell sarcoma may be derived, and the other a reticulum cell framework, from which the reticulum cell sarcoma or "retothelsarcoma," as he termed it, may arise According to Aschoff, Downey and Maximow,⁶ the primitive mesenchymal cell of embryonic life is the mother cell for all the types of mature cells which comprise a lymph node

In this paper an attempt has been made to divide lymphosarcomas of the stomach as nearly as possible into the two types (1) reticulum cell sarcoma (large round cell lymphosarcoma) and (2) malignant lymphocytoma (small round cell lymphosarcoma) An attempt has been made to analyze reticulum cell sarcomas clinically and morphologically and to make some comparisons between them and malignant lymphocytomas Although this differentiation is not commonly made, it is practical and of clinical importance, for the two types differ in their response to roentgen therapy According to Krumbhaar⁷ and others, the reticulum cell sarcoma shows greater resistance to roentgen therapy than does the malignant lymphocytoma

To afford a better understanding of the pathogenesis of and the symptoms produced by the reticulum cell sarcoma, we shall sketch briefly the anatomy of the lymphatic vessels of the stomach⁸ The lymphoid tissue in the stomach is much like that of the intestines The lymphatic vessels arise from a well developed system of capillaries in the most superficial layer of the mucous membrane, between the glands, a layer somewhat deeper than the capillaries of the blood There is considerable anastomosis throughout the mucous membrane, from which these lymphatic channels extend toward the serosa and form a plexus on the deep surface of the mucosa From that region the lymphatic vessels extend deeper, through the muscularis mucosae into the submucosa, where the lymph follicles are situated The lymphatic vessels extend from here through the deep layers of muscles of the stomach and terminate in the retroperitoneal lymph nodes Each lymph nodule, or follicle, consists of dense groups of lymphocytes supplied by a blood

5 Roulet, F (a) Weitere Beiträge zur Kenntnis des Retothelsarkoms der Lymphknoten und anderer Lymphoiden-Organe, *Virchows Arch f path Anat* **286** 702-732, 1932, (b) Das primäre Retothelsarkom der Lymphknoten, *ibid* **277** 15-47, 1930

6 Aschoff, Downey and Maximow, cited by Hasselmann, C M Retothel-Sarcoma Among Filipinos in the Tropics, *Philippine J Sc* **54** 1-5 (May) 1934

7 Krumbhaar, E B The Lymphatoid Diseases, *J A M A* **106** 286-291 (Jan 25) 1936

8 (a) Maximow, A A, and Bloom, W A Text Book of Histology, Philadelphia, W B Saunders Company, 1930 (b) Piersol G A Normal Histology ed 15, Philadelphia J B Lippincott Company 1932 p 191

vessel and surrounded by a framework of connective tissue. In the center of the active follicle is a portion which stains lighter than the rest, the secondary follicle, which is made up of less mature lymphocytes, throughout which are scattered primitive reticular cells with indistinct cytoplasm. While the primary follicle is at rest, the secondary follicle is apparent only as a small artery surrounded by a few nuclei of the primitive reticular cells in the center of the primary follicle.

The material used for study consisted of all specimens of sarcoma of the stomach available for study at the Mayo Clinic. There were 67 such specimens, which could be apportioned as indicated in table 1.

The incidence contained in table 1 is in accord with results of studies made by other authors, however, in some series the classification is so variable that it is difficult to draw comparisons. Most authors concur in the opinion that lymphosarcoma is the most common form of sarcoma found in the stomach. Pack and McNeer⁹ expressed the

TABLE 1—*Types of Sarcomas Represented in Sixty-Seven Cases of Sarcoma of the Stomach Encountered at the Mayo Clinic*

Lesion	Cases	Per Cent
Lymphosarcoma (41, or 62 per cent)		
1 Reticulum cell sarcoma	20	30
2 Malignant lymphocytoma	21	32
Hodgkin's sarcoma	6	8
Leiomyosarcoma	7	11
Fibrosarcoma	9	13
Mixed group	4	6
Total	67	100

opinion that of the two types of lymphosarcoma arising in the stomach practically all lesions are of the reticulum cell variety and only a few are of the malignant lymphocytoma type. Our series shows that the two types are of approximately equal incidence, with the small cell lymphosarcoma (malignant lymphocytoma) in slight preponderance.

CAUSATIVE BACKGROUND

The cause of lymphosarcoma of the stomach is unknown. We shall not review the speculations that have been offered, and there was nothing derived from this study to add to existent theories.

MORPHOLOGIC ASPECTS

In this series the typical morphologic picture of reticulum cell sarcoma (fig. 1A) was one in which the lymph follicles were invaded and destroyed by large, pale cells, with nuclei of bizarre configuration, most

9 Pack, G. T., and McNeer, G. Sarcoma of the Stomach. Report of Nine Cases, *Ann. Surg.* **101**: 1206-1224 (May) 1935.



A, section of reticulum cell sarcoma of the stomach, with large pale cells containing nuclei of bizarre configuration. The nucleoli are not prominent; chromatin is finely divided and characteristically the tumor shows a loose cellular structure. Hematoxylin and eosin $\times 1100$. *B*, malignant lymphocytoma (small round cell lymphosarcoma) showing wild proliferation of mature lymphocytes. Nucleoli are more prominent and chromatin more heavily distributed than in reticulum cell sarcoma, with a very compact arrangement of the cells. Hematoxylin and eosin, $\times 1,100$.

of which were round, oval, reniform and horseshoe shaped. These nuclei were two to three times the size of those seen in the malignant lymphocytoma (fig 1 B). The cells were larger than immature lymphocytes, and some evidence of phagocytosis was observed. Nucleoli were not prominent, and the chromatin was diffusely dusted throughout the nuclear substance. The cytoplasm was somewhat eosinophilic and was considerable in amount. There was no evidence of formation of reticulum, as determined by the Galantha modification of Bielschowsky's silver impregnation method. Throughout the tumors there were varying numbers of small mature lymphocytes, and the cells were not always uniform in size or shape. Some portions were rather compact, but in most sections the cellular structure was loose. In regions where connective tissue was present, the tumor cells were seen to have their long axes parallel to the long axes of the fibers of connective tissue.

The infiltrative quality of the tumor cells was notable, and the muscular tissues as well as the capsules of the involved lymph nodes were frequently penetrated and destroyed. In some sections, invasion of blood vessels was also noted. The structure of the involved lymph nodes was identical with that of the primary tumor in the stomach.

The absence of reticulum is a characteristic consistent with the observations of Richter¹⁰ and Gall¹¹. In reviewing cases of malignant lymphoma of the stomach at the Massachusetts General Hospital, Gall noted the absence of formation of reticulum. It is known that tumor cells do not necessarily carry on the functions of the tissues from which they arise. It has been suggested by Kaufmann and Ribbert¹² that demonstration of reticulum is facilitated by washing out the cells. This procedure, however, could not be followed in any of our studies.

DIFFERENTIAL DIAGNOSIS

Tumors which might be confused with reticulum cell sarcoma are (1) malignant lymphocytoma, (2) Hodgkin's disease, (3) very cellular carcinoma, (4) endothelioma, (5) hyperplastic noncaseous tuberculosis and (6) giant follicle lymphoma (giant follicle hyperplasia).

The malignant lymphocytoma, or small round cell lymphosarcoma, is a tumor in which the involved lymphoid tissue is destroyed by lymphocytes, usually immature, and in which the capsule and adjacent tissues are invaded. It may or may not be associated with lymphatic leukemia. Usually there is little fibrosis and no eosinophilia. If plasma cells, eosinophils and normal lymphocytes are present, an inflammatory lesion must be considered.

10 Richter, M. N. Generalized Reticular Cell Sarcoma of Lymph Nodes Associated with Lymphatic Leukemia, *Am J Path* 4: 285-292 (July) 1928.

11 Gall, E. A. Personal communication to the authors.

12 Kaufmann and Ribbert, cited by Ewing,⁴ p. 414.

The picture seen in Hodgkin's disease is variable, depending largely on the stage of the development of the lesion. Dorothy Reed¹³ has established the typical picture as it is known today. Hodgkin's disease is characterized morphologically by marked proliferation of lymphocytes, large and small, and by proliferation of endothelium with the formation of endothelial giant cells, varying numbers of eosinophils, plasma cells and fibroblasts. Early in the disease lymphocytes predominate with an associated endothelial cellular proliferation and some fibroblastic reaction. According to Bunting,¹⁴ the early lymphocytic stimulation is followed by a destructive action on these cells. As the disease progresses, the fibroblastic proliferation increases, and transitions from endothelial cells to giant cells soon occur. These giant cells may be either uninuclear or multinuclear (Sternberg-Reed) giant cells. Eosinophils are seldom absent but are not pathognomonic of this lesion. Bunting maintained that they may occur in any condition in which there is lymphocytic destruction. The 6 cases of Hodgkin's disease of the stomach encountered in this study were reported by one of us (Madding¹⁵).

At times it is impossible to differentiate absolutely a very cellular carcinoma from a reticulum cell sarcoma. Alveolar and glandular arrangements, the relationship of the long axis of the cells to strands of connective tissue, the presence and size of nucleoli and the presence of mucus in the tumor are factors aiding in this differentiation. When we stained reticulum cell sarcomas by the Galantha method for mucin, we found no evidence of this substance.

Endothelioma of lymphoid tissue at times may be indistinguishable from reticulum cell sarcoma. Although the endothelial cell is ordinarily a large, flat cell with a large, oval nucleus, it may assume many shapes when found in the tumor. The endothelial cells are often found arranged in sheets or cords, and tumors arising from these cells not only are very rare but are much less malignant than sarcomas. There is often a definite relationship of the tumor cells to the endothelium of the sinuses and blood vessels. This tumor is rather radiosensitive and is thus greatly in contrast to the reticulum cell sarcoma.

Chronic hyperplastic noncaseous tuberculosis (Boeck's sarcoid), although rare, may produce symptoms confusing to one attempting a differential diagnosis morphologically. It closely resembles reticulum cell sarcoma, but certain characteristics of the sarcoma, namely, the large endothelial cell proliferation, the presence of giant cells and the absence

13 Reed, D. On the Pathological Changes in Hodgkin's Disease, with Especial Reference to Its Relation to Tuberculosis, *Johns Hopkins Hosp. Rep.* **10** 133-196, 1902.

14 Bunting, C. H. Diseases of the Lymph Glands, in Nelson New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1937, vol. 3, pp. 347-368.

15 Madding, G. F. Hodgkin's Disease of the Stomach. Report of Six Cases, *Proc. Staff Meet., Mayo Clin.* **13** 618-623 (Sept. 28) 1938.

of lymphocytic hyperplasia, are factors aiding in the diagnosis. In difficult cases resort may be had to inoculation of guinea pigs.

In giant follicle lymphoma there is seen in both the cortex and the medulla a diffuse distribution of the germinal centers composed of pale, uniform cells of uncertain origin. The absence of necrosis, of polymorphonuclear leukocytes and of phagocytosis serves to distinguish the condition from that of a purely inflammatory lesion. Giant follicle lymphoma is a relatively benign form of malignant lymphoma, as shown by the dearth of mitotic figures, and is one of the particularly radio sensitive types of tumors. However, some patients with this lesion present the terminal picture of a patient who has lymphosarcoma.

CLINICAL FEATURES

Age—Reliance on age of the subjects in studying the incidence of reticulum cell sarcoma of the stomach is as dangerous as in studying that of gastric carcinoma. Reticulum cell sarcoma of the stomach is a disease of later life, the average age of the patients being 46.7 years. Our graphs showed that the peak of the incidence occurs between 40 and 49 years and that 70 per cent of the tumors occur between the fourth and the seventh decade. The youngest patient was 22 years old, and the oldest, 66. These figures agree closely with those for malignant lymphocytoma, with the exception that in graphs of lymphocytoma the peak of incidence is in the sixth decade. In our series the average age for the entire group of patients with sarcoma of the stomach was 50.2 years. Balfour and McCann¹⁶ reported the average age of patients with carcinoma of the stomach as 61—in other words, that there is a difference of 14.3 years between the average age of patients suffering from reticulum cell sarcoma of the stomach and the average age of patients having carcinoma of the same organ.

Sex—Sex, too, played a part in the incidence of reticulum cell sarcoma, men outnumbering women 6:1. Cheever¹⁷ and Douglas¹⁸ stated the opinion that gastric sarcoma is evenly distributed between the sexes, but throughout the entire group of sarcomas of the stomach reviewed at the clinic tumors among men predominated.

REGIONAL DISTRIBUTION

In the cases which we studied reticulum cell sarcoma was found most often on the lesser curvature and on the posterior wall of the stomach, the regions in which the majority of all malignant lesions of the stomach

16 Balfour, D. C., and McCann, J. C. Sarcoma of the Stomach, *Surg., Gynec. & Obst.* **50**: 948-953 (May) 1930.

17 Cheever, D. Clinical Aspects and Treatment of Primary Lymphosarcoma of the Stomach and Intestines, *Ann. Surg.* **96**: 911-923 (Nov.) 1932.

18 Douglas, J. Sarcoma of the Stomach, with Report of Three Cases, *Ann. Surg.* **71**: 628-636 (May) 1920.

are found. This observation is not in keeping with the opinion expressed by Lubarsch and Henke,¹⁹ that sarcoma seldom occurs on the lesser curvature. The percentages of the commoner sites of occurrence of both reticulum cell sarcomas (large round cell lymphosarcomas) and malignant lymphocytomas (small round cell lymphosarcomas) are contained in table 2.

SIGNS, SYMPTOMS AND LABORATORY OBSERVATIONS

Sarcoma of the stomach presented no typical picture, and only a few of the patients had the classic history for neoplastic involvement of the stomach. A short history presented by a previously healthy person proved more valuable for diagnosis than specific symptoms of a non-malignant condition. The symptoms, of course, depended on the size and site of the lesion, on the type and extent of the growth and on the patient's reaction to a departure from his normal condition.

TABLE 2—*Site of Occurrence (by Percentage) of Reticulum Cell Sarcoma and Malignant Lymphosarcoma of the Stomach*

Site	Type of Sarcoma	
	Reticulum Cell, per Cent	Malignant Lymphocytoma per Cent
Lesser curvature	25	25.8
Posterior wall	25	9.5
Pylorus	15	9.5
Greater curvature	10	4.8
Cardiac portion	10	0.0

According to our observations, the reticulum cell sarcoma arises from the reticular cells of the lymph follicles in the submucosa, spreads from there by permeation and invades the various layers of the stomach. Since the sarcoma originates in the submucosa, the mucosa itself is not early involved and ulceration does not occur in sarcoma of the stomach as soon as it does in carcinoma of the stomach. Because of the proximity of the sarcoma to the submucous plexus of nerves, pain is a very common feature. In all the cases of reticulum cell sarcoma studied, pain was present, either generalized throughout the abdomen or, more often, localized in the midepigastrium. In some instances the history was like that typical of peptic ulcer. The pain, however, did not respond as well to the usual treatment of ulcers and was not periodic, as that of ulcers often is. Some patients complained of belching, anorexia, epigastric nocturnal pain and loss of weight and strength. Six of the 21 patients complained of vomiting, which in 3 instances was caused by involvement of the pylorus by the neoplasm. In 1 case only was gross

¹⁹ Lubarsch, O., and Henke, H. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 4, pt. 1.

blood noted in the stool Reticulum cell sarcoma does not show large masses projecting into the leaves of the omentum or into the free peritoneal cavity, as fibrosarcoma and leiomyosarcoma Consequently, a palpable tumor was not often found

The duration of symptoms of reticulum cell sarcomas ranged from two months to several years, but as a rule the course was shorter than that of malignant lymphocytoma or carcinoma The average duration of symptoms of reticulum cell sarcoma in inoperable patients was thirty-seven months In 20 per cent of the cases the family history indicated a background of malignancy Although there was always loss in weight, it varied in amount, the mean loss being 25 pounds (about 11 Kg)

Gastric analysis (Topfer's test) showed achlorhydria in 67 per cent of the cases of reticulum cell sarcoma, normal acids in 20 per cent, and free acid but in subnormal amounts in 13 per cent The blood picture was of the type associated with other tumors involving the stomach, but the anemia was not as extreme as it is in the presence of carcinoma of the stomach This is perhaps due in part to delayed ulceration of the sarcomatous lesions The anemia that we observed was of the microcytic hypochromic type, with a hemoglobin content averaging 84 per cent and a mean erythrocyte count of 4,500,000 The leukocyte counts were normal, averaging 8,200 There were not sufficient differential determinations of leukocytes from which to form any conclusions (It is interesting to note that in 1 instance an associated lymphatic leukemia was found to afflict a patient who had generalized reticulum cell sarcoma of the lymph nodes) The temperature was normal in all cases but 2, in which readings of 99 and 99.6 F were recorded at the time of the initial examination

DIAGNOSIS BY ROENTGEN EXAMINATION

Since roentgen examination failed to lead to the correct diagnosis in any of the cases, it seems reasonable to conclude that roentgenographically there are no absolutely diagnostic characteristics of the lesion The roentgen diagnosis most often made was "carcinoma," but the roentgenographic examination was important as giving an index to the operability of the lesion Holmes, Dresser and Camp²⁰ expressed the opinion that there is nothing diagnostic in the roentgenographic appearance of lymphosarcoma of the stomach, but said that in some cases of lymphosarcoma peristalsis is not interfered with as much as in most cases of carcinoma of the stomach This group of reticulum cell sarcomas of the stomach were diagnosed by roentgen examination as carcinoma in 15 cases and as ulcer in 2 cases The condition was pro

20 Holmes, G W , Dresser, R, and Camp, J Lymphoblastoma, *Radiology* 7 44-50 (July) 1926

nounced normal in 1 case and in 2 cases no examination was made. According to Schlesinger,²¹ a stomach involved by sarcoma will not dilate during insufflation, but there is no reason to believe that a stomach diffusely involved by scirrhous or mucous carcinoma would dilate under similar circumstances.

METASTASIS

The manner and route of dissemination of reticulum cell sarcoma depend largely on the location of the tumor in the stomach. The spread is achieved usually by the lymphatic system, but we observed evidence of invasion of the blood vessels in some sections. Because the sarcoma often occurs on the lesser curvature of the stomach, the lymphatic vessels which drain toward the liver are usually involved after the perigastric lymph nodes have been invaded. Metastatic lesions occurred in 65 per cent of the cases of reticulum cell sarcoma and in 70 per cent of the cases of malignant lymphocytoma. Flebbe²² gave the following list to show the order of frequency in which the various organs are affected by metastasis: regional lymph nodes, liver, mesentery, colon, peritoneum, omentum, ovary, pancreas, bones, pleura, lung, testicle, spleen, diaphragm, kidney, adrenal and skin.

TREATMENT AND PROGNOSIS

Surgical treatment has more to offer to patients having sarcoma of the stomach than to those having carcinoma. Until the advent of radiation therapy, the treatment was the same for the two conditions, namely, an attempt at radical extirpation. Our studies showed that of patients with reticulum cell sarcoma 90 per cent resorted to operation, of those with malignant lymphosarcoma, 66 per cent. Among patients having both types of lymphosarcoma encountered at the clinic, the percentage of operations was higher than among patients having carcinoma of the stomach, according to Ranschoff and Dickson.²³ The patients whose reticulum cell sarcoma was treated by surgical procedures alone had an average life span of three and thirty-eight hundredths years, as contrasted with three and thirty-one hundredths years for those on whom radiation therapy was used as an adjunct. In neither of these groups were patients included who died of postoperative complications (pneumonia, peritonitis and embolus). Of the entire group of patients who had reticulum cell sarcoma of the stomach and who were treated at the clinic, 41 per cent are still living, the longest survival period for any

21 Schlesinger, H. Unterscheidet sich das Magensarkom klinisch von Karzinom? *Wien klin Wchnschr* **29** 785-791, 1916.

22 Flebbe, G. Ueber das Magensarkom, *Ztschr f Path* **12** 311-336, 1913.

23 Ranschoff, J. L., and Dickson, T. R. Sarcoma of the Stomach, *Ann Surg* **97** 68-73 (Jan) 1933.

patient in this group was fifteen years at the time the person was last heard from. The duration of life was directly related to the presence or absence of involvement of the lymph nodes. As with carcinoma, the grade of malignancy of the tumor and the amount of involvement of lymph nodes, which closely parallels the malignancy, were the two important factors in determining the prognosis. Of the reticulum cell sarcomas, 65 per cent were found at the time of operation to have involved the lymph nodes. The life span of the group of patients with such involvement was two and seventy-nine hundredths years, as compared with four and eight-tenths years for the group of patients having no involvement of the lymph nodes. Age and sex played no part in the prognosis for this group.

In comparing the figures for the group of patients having reticulum cell sarcoma with those for the group having malignant lymphocytoma, one finds that the latter have the better life expectancy. The patients having malignant lymphocytoma who were treated by surgical means alone had an average life of five and six-tenths years postoperatively, as contrasted with three and sixty-five hundredths years for those treated by surgical intervention followed by irradiation. Of the patients with malignant lymphocytoma, 56 per cent were still living when last heard from. Two of these patients were living and well fourteen years after their operation. One died seven years postoperatively of pyelonephritis, at necropsy no evidence of the tumor was found. For only 1 of the patients, who achieved a fourteen year cure, was roentgen therapy used in addition to a surgical procedure.

From the aforementioned statistics, one obtains the impression that a patient having malignant lymphocytoma (small round cell lymphosarcoma) has a better prognosis than does a patient having reticulum cell sarcoma. This idea conflicts with the opinion expressed by Jackson,²⁴ who, in a general discussion of the lymphomatoses of the body without special reference to the stomach, said that reticulum cell sarcoma remains localized for a longer period than malignant lymphocytoma and that prompt surgical removal makes possible a longer survival for some patients.

On the reactivity of the two types of tumor cells to roentgen therapy, there seems to be some uniformity of opinion. Krumbhaar⁷ and Lalung-Bonnaire and Bablet²⁵ stated the opinion that reticulum cell sarcomas are more resistant to this form of therapy than are malignant lymphocytomas. In the cases of reticulum cell sarcoma of the stomach encoun-

24 Jackson, H. The Classification and Prognosis of Hodgkin's Disease and Allied Disorders, Surg, Gynec & Obst **64** 465-467 (Feb) 1937.

25 Lalung-Bonnaire and Bablet. A propos des sarcomes ganglionnaires du cou les tumeurs d'origine reticulo-endotheliales, Presse med **2** 1194 (Sept 5) 1925.

tered at the clinic roentgen therapy seemed to play no part in increasing the life expectancy. This seemed true also in the group of patients having malignant lymphocytoma, in that group the patients given only surgical treatment lived an average of one and ninety-five hundredths years longer than those given both surgical and roentgen therapy. However, of the patients receiving both surgical treatment and roentgen therapy, 83 per cent had glandular involvement. Of the patients having malignant lymphocytomas and receiving only surgical treatment, only 65 per cent had glandular involvement. Thus, one may see that the group of patients to whom roentgen therapy was given as a supplement to surgical treatment had from the beginning a poorer prognosis, because of the more extensive involvement.

Of the group of patients having malignant lymphocytoma, 6 were found to be inoperable. On 3 of them roentgen therapy was used, with the result that 1 patient was living and well two and one-half years after the roentgen therapy was given and the other 2 lived an average of two and two-tenths years. The other 3 patients with inoperable malignant lymphocytoma, who did not receive any form of treatment, were dead within four months.

Of the 2 patients having reticulum cell sarcoma which was found to be inoperable, 1 was given roentgen therapy and died on the way home, the other, who received no treatment, died four months post-operatively, of hemorrhage.

Another interesting feature of our series was the comparison of the prognosis for reticulum cell sarcoma and malignant lymphocytoma with that of other sarcomas of the stomach. According to D'Aunoy and Zoeller,²⁶ pedunculated or spindle cell sarcoma, with which they included leiomyosarcoma and fibrosarcoma, has a better prognosis than the infiltrating type of sarcoma, which includes the reticulum cell sarcoma and the malignant lymphocytoma. This was not true of the group of sarcomas encountered at the clinic. In our series the average life span for patients having spindle cell sarcoma was three and three-tenths years, only 1 patient being inoperable at the time of exploration. The average life span of patients having reticulum cell sarcoma and malignant lymphocytoma was three and ninety-eight hundredths years.

These observations are supported by the opinions expressed by Jones and Carmody²⁷ and also by Collins,²⁸ all of whom found that

26 D'Aunoy, R, and Zoeller, A. Sarcoma of the Stomach. Report of Four Cases and Review of the Literature, *Am J Surg* **9** 444-464 (Sept.) 1930.

27 Jones, T. E, and Carmody, M. G. Lymphosarcoma of Stomach. Report of Case with Nineteen-Year Surgical Cure, *Ann Surg* **101** 1136-1138 (April) 1935.

28 Collins, E. N, and Carmody, M. G. Lymphosarcoma of Stomach. Report of Four Cases, *Am J Digest Dis & Nutrition* **3** 884-888 (Feb.) 1937.

patients having round cell lymphosarcoma comprised the greatest number of those surviving the five year period. The case reported by Jones and Caimody was one of lymphosarcoma of the stomach, the patient was living and well nineteen years postoperatively—the longest survival period of any patient having sarcoma of the stomach reported in the literature.

Among the patients encountered at the clinic, 56 per cent of those who had malignant lymphocytoma are still living, as compared with 41 per cent of those who had reticulum cell sarcoma. Eighteen per cent of the patients who had leiomyosarcomas are still living, and 62 per cent of those who had fibrosarcomas. The number of patients in this series is perhaps too small to permit formation of any statistical conclusions.

In connection with this consideration of the results obtained in treating with roentgen therapy patients having inoperable lymphosarcoma, it is interesting to note the classic experimental work of Heineke,²⁹ who demonstrated well the effect of radiation on various tissues of the body. Numerous animals were irradiated for varying periods and then killed, sections of all tissues were immediately made. It was the lymphoid tissue which responded first and most markedly to this irradiation. The lymphocytes bordering the follicles were the first to disintegrate, and these were replaced by epithelial cells. The clear, large cells in the center of the lymph follicles did not disintegrate, but seemed to become phagocytic. These epithelioid cells were of questionable origin. Heineke stated the belief that they were derived from the supporting structure of the lymph node. Ribbert, Zeigler and Kaufmann³⁰ declared that they were transformed endothelium of the supporting tissue of the lymph node. Councilman, Mallory and Pearce³¹ said that they were proliferated endothelium of the reticulum.

COMMENT

Review of the cases of reticulum cell sarcoma and malignant lymphocytoma encountered at the Mayo Clinic confirms the general impression that lymphosarcoma is an uncommon condition but contrasts with the general opinion that the two tumors have a better prognosis than leiomyosarcoma and fibrosarcoma. Reticulum cell sarcoma and malignant lymphocytoma are as insidious in their development as carcinoma, and neither lesion seems to offer a greater probability of reaching the surgeon in an early and operable stage.

29 Heineke, H. (a) Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf innere Organe, *Mitt a d Grenzgeb d Med u Chir* **14** 21-94, 1905, (b) Ueber die Einwirkung der Röntgenstrahlen auf Tiere, *Munchen med Wchnschr* **50** 2090-2092 (Dec 1) 1903.

30 Ribbert, Zeigler and Kaufmann, cited by Heineke ^{29a}.

31 Councilman, Mallory and Pearce, cited by Heineke ^{29a}.

In the stomach, the radical operability was low, and differential diagnosis to distinguish lymphosarcoma from carcinoma was impossible. On the basis of the histories at the clinic, it seemed safe to conclude that both reticulum cell sarcoma and malignant lymphocytoma remain localized for some time. Thus, a radical cure by total extirpation is possible, and this should be the goal in every instance.

It seemed evident from the malignant lymphocytomas which were found to be inoperable that irradiation played a part in prolonging the life of the patients. This, however, was not true of the inoperable reticulum cell sarcomas, of which there were only 2. It would seem, on the strength of this survey of a group of patients having sarcoma of the stomach, that it is highly desirable and practicable to perform an exploratory operation and to obtain a biopsy specimen, even for patients concerning whom the clinical evidence points strongly to the presence of an inoperable growth. A differentiation of the two types of so-called lymphosarcoma may then be made, and patients having malignant lymphocytoma (small round cell lymphosarcoma) may be given the benefit of roentgen therapy.

Borzell³² suggested the use of radiation therapy for patients with lesions clinically found to be inoperable, with the hope of reducing the size of the lesion in a certain percentage of cases. In other words, pre-operative intensive irradiation probably would convert an inoperable lesion into one in the stage of operability. Above all, it seems important to differentiate the two types of lymphosarcoma, so that adequate evidence may be accumulated as to the exact histologic type of neoplasm which can be benefited by roentgen therapy.

CONCLUSIONS

Sixty-seven cases of sarcoma of the stomach were studied, of which group 30 per cent were cases of reticulum cell sarcoma (large round cell lymphosarcoma) and 32 per cent of malignant lymphocytoma (small round cell lymphosarcoma).

Morphologically, reticulum cell sarcoma is characteristic. The typical cells are large and pale, with nuclei of bizarre configuration, most of which are round, oval, reniform or horseshoe shaped. Nucleoli are not prominent, and the chromatin is diffusely dusted throughout the nuclear substance. There is no evidence of formation of reticulum.

Conditions which might be confused morphologically with lymphosarcoma are (1) malignant lymphocytoma, (2) Hodgkin's disease,

³² Borzell, F. F., in discussion on Drane, R. A Brief Consideration of Sarcoma of the Stomach. Report of a Case of Primary Lymphosarcoma, *Am J Roentgenol* **34** 757-758 (Dec.) 1935.

(3) very cellular carcinoma, (4) endothelioma, (5) noncaseous tuberculosis and (6) giant follicle lymphoma

Clinically, it is impossible absolutely to differentiate reticulum cell sarcoma from other neoplastic lesions involving the stomach

Treatment of lymphosarcoma of the stomach should be surgical removal when possible, with roentgen therapy used as an adjunct in the treatment of the malignant lymphocytoma

Prognosis for the combined group of lymphosarcomas of the stomach is better than it is for carcinoma involving this organ. The entire group of lymphosarcomas of the stomach observed by us had a better prognosis than did the group of leiomyosarcomas and fibrosarcomas

It is practicable to differentiate the two types of lymphosarcoma of the stomach, because of the morphologic variation and also because if differentiation is made, adequate evidence may be accumulated as to the exact histologic type of neoplasm which may be benefited by roentgen therapy

PRIMARY CARCINOMA OF THE TERMINAL PORTION OF THE COMMON BILE DUCT

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BROOKLYN

It is proposed to present in this paper some of the salient features of carcinoma of the terminal portion of the common bile duct with special reference to its pathologic picture and atypical symptoms. The following observations are based on 17 cases of carcinoma of this area collected from the records of the Jewish Hospital. In 8 of these cases necropsy was performed, which allowed us a more detailed study of the pathologic changes. Analysis of the case histories was instigated by the considerable literature on the subject which has accumulated within recent years, and some of the striking features that became manifest from this analysis are the following interesting facts: first, the discovery in a relatively large percentage of cases of an acute inflammatory process of the gallbladder as the outstanding characteristic at or about the time of the first examination, second, the frequent finding of concomitant changes in organs adjoining the bile duct, which gave rise to symptoms that overshadowed at times those produced by the primary lesion in the bile duct and rendered clinical diagnosis difficult.

It is not within the scope of this paper to review in detail the etiology, pathology and symptoms of carcinoma of the bile duct, as this information is readily available in any of the numerous publications on the subject, but rather to discuss a few of the more salient factors which should be borne in mind when one is called on to treat this condition. An analysis of the voluminous literature on carcinoma of the bile duct has been presented in an admirable paper by Lieber, Stewart and Lund.¹ The historical phase, therefore, has been deleted from this paper.

We wish to state at the outset that the present study is concerned with neoplasms confined to the terminal portion of the common bile duct, including the ampulla and the papilla of Vater. It is not concerned with lesions arising from the duct above the duodenum or with tumors arising from the duct of Wirsung or the duodenum.

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1 Lieber, M. M., Stewart, H. L., and Lund, H. Carcinoma of the Peripapillary Portion of the Duodenum, *Ann Surg* 109:383 (March) 1939.

The clinical manifestations of carcinoma of the terminal portion of the bile duct are subject, by reason of the anatomic peculiarities of the part, to many variations. The close proximity of the duodenum to the bile duct and the close anatomic relation which exists between the pancreas, liver and gallbladder as their ducts meet in this narrow zone of the bile duct is responsible for the secondary pathologic changes and clinical complications that are apt to occur in cases of this condition. The same anatomic relation of these structures permits a great variety of symptom complexes even in the presence of a trivial lesion in the duct. It is well to bear in mind also that the site in which symptoms first appear is not necessarily that in which the disease develops. Thus, a growth situated at the point of entry of the common bile duct and the pancreatic duct into the ampulla causes interference with the outflow of biliary and pancreatic secretions into the duodenum, this in turn gives rise to far-reaching pathologic changes in the liver, gallbladder and pancreas and causes symptoms peculiar to the organ thus affected. Occasionally, too, the growth in the duct is accompanied by calculous deposits in the biliary and pancreatic ducts, or the ductal growth may invade the duodenum and cause necrosis and ulceration of its wall. Such complicating factors give rise to a rather misleading clinical picture and render diagnosis difficult. In summary it may be said that the symptoms of carcinoma of the terminal portion of the bile duct are not entirely dependent on factors inherent in the growth itself but are influenced also by a variety of other factors, the most important of which are the anatomic configuration of the part affected, the type and location of the tumor, the extent of dissemination of the tumor and the secondary inflammatory changes which so often form part of the pathologic picture.

AGE AND SEX

The ages of the patients in this series ranged from 38 to 68, averaging 56.5. These figures are in accord with the records collected from the literature, and they are also in harmony with the general incidence of cancer of any organ of the body. There were 12 men and 5 women, a ratio of approximately 2:1.

ANATOMIC CONSIDERATIONS

As carcinoma of the bile duct is closely related to the histologic structure of the duct, it will be necessary to restate the cardinal features of the old and new concepts of its minute anatomy, with special emphasis on these aspects that are relevant to the purpose of this paper.

Kiernan,² as early as 1833, first described accessory glandlike structures within the walls of the bile ducts which communicate with

² Kiernan, F. *The Anatomy and Physiology of the Liver*, Phil. Tr., London 123:711, 1833.

the lumen by numerous minute orifices. Several years later, Theile³ showed that these structures consist of branching clusters terminating frequently in small cecal diverticula, he considered them to be small mucous glands. Beale⁴ was the first to use the term parietal saccule for the mucous glands of Kiernan and Theile, he considered them ductal diverticula rather than mucous glands and found that they occurred not only in the common and hepatic bile ducts but within the smaller ramifications of the intrahepatic bile ducts. In most textbooks on histology these saccules are referred to as glands of the ducts. From a number of serial sections of the normal distal portion of the common bile duct which we recovered at necropsy shortly after death, the only structures present in the walls of the ducts which might be interpreted as mucous glands are the parietal sacculi. These structures, when sectioned at levels not showing their communication with the lumen of the main duct, resemble glandular elements. According to Cox,⁵ they are not to be considered as true glands, for both anatomic and physiologic reasons. He showed that in the case of biliary obstruction of whatever cause these sacculi dilate in the same fashion as do the bile ducts and that their epithelial lining exhibits the same fat-absorptive property as does that of the epithelium of the bile ducts and gallbladder. This investigator concluded, therefore, that there are no such structures as true mucous glands of the bile ducts. It is true that their epithelium secretes mucus, but the same holds true in the case of epithelium of the ducts and of the gallbladder. Besides, they never contain mucus in any greater amount than do the cells covering the main ducts and the gallbladder (fig 1).

The view held by Cox is analogous to the view we have expressed, although we seem to differ in one respect, namely, that in addition to the aforementioned changes we have noted in the normal bile duct villous structures which project from the surface mucosa into the lumen. As we understand, or perhaps misunderstand, the conclusions of Cox similar villus-like folds were described by him to be present only in pathologic bile ducts, he considered them to be the walls or lips of dilated sacculi which appear in cases of biliary obstruction.

3 Theile. *Die Leber*, in Wagner, R. *Handwörterbuch der Physiologie*, Braunschweig, F. Vieweg u. Sohn, 1842-1853, vol. 2, pp. 349-351.

4 Beale, L. S. *On Some Points in the Anatomy of the Liver of Man and Vertebrate Animals*, London, John Churchill, 1856, pp. 31-80, *Lectures on the Principles and Practice of Medicine. The Liver*, London, J. & A. Churchill, 1889.

5 Cox, F. W. *Changes in the Bile Ducts and Parietal Sacculi Following Absence of the Gall Bladder*, *Surg., Gynec. & Obst.* **55** 168 (Aug.) 1932.

PATHOGENESIS

The following observations are based on a series of 8 cases of carcinoma of the terminal portion of the common bile duct in which necropsy was performed. Grossly, the tumor was either a small, soft friable papillary lesion or a firm, nodular growth which caused partial or complete obstruction of the bile duct. The sectioned surfaces were usually gray. The size of the tumor was determined in all 8 cases, the largest growth measuring 4 by 3 cm and the smallest 5 mm in

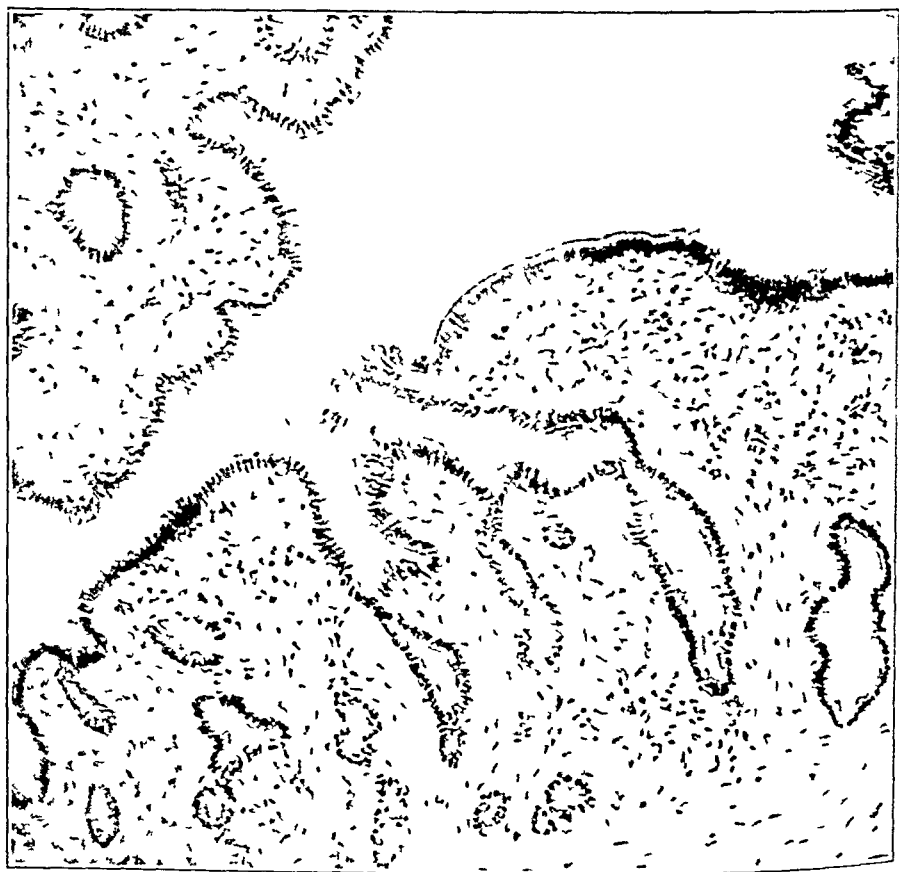


Fig 1—Section of the normal bile duct close to the ampulla. The lining epithelium, which is of the tall columnar type, shows numerous diverticula which become detached in places and give rise to glandlike structures (sacculi) embedded within the wall of the duct.

diameter. In certain instances the primary tumor in the duct was of insignificant size and appearance, yet its invasion into adjoining structures, such as the duodenum, was extensive. It was difficult to decide in these cases which was the primary and which the secondary lesion. The size of the tumor was not conclusive evidence, for a secondary growth may be larger than the primary growth. In 1 instance a

primary carcinoma of the ampulla was erroneously diagnosed as primary in the duodenum, but microscopic examination of the specimen proved it to be of ductal origin. The symptoms of carcinoma of the two organs are similar, although carcinoma of the ampulla probably gives rise to symptoms earlier than does a lesion of the duodenum.

In only 1 of the 8 cases was the ampulla sufficiently dilated to allow free escape of bile into the duodenum. When the growth had caused partial or complete blockage to the outflow of bile there occurred various degrees of dilatation of the biliary channels, including the gallbladder. In 1 case the common bile duct was so dilated as to be mistaken at first sight for the gallbladder. Accompanying the dilatation of the ducts there was generally found an associated inflammatory reaction.

Microscopically, all the tumors stained with hematoxylin and eosin showed a strikingly morphologic similarity to the normal parietal sacculi lying within the wall of the bile duct. The epithelium of the growth was in general of the tall columnar type, and the structure was that of an adenocarcinoma. There were acini and tubules lined by columnar cells and set in a stroma of relatively dense fibrous connective tissue. Evidence of secretory activity of these cells was furnished by the presence of mucin within the cellular cytoplasm and within the acini. Many of the cells contained small droplets of mucin in their cytoplasm, and some of them were swollen to signet ring shape by a large globule of this substance, which distended the cell and forced the nucleus to one edge. A cell thus distended may burst, discharging its mucinous content into the lumen or into the connective tissue spaces (fig. 2).

In most cases the cells were obviously malignant, but in others the appearance was not greatly different from that of the normal cells of the mucosa and the parietal sacculi. In cells free of mucin the nuclei were relatively large, deeply stained and basally placed, leaving a peripheral, somewhat palely stained granular cytoplasm. Mitotic figures were relatively few, which designated a low degree of malignancy. The stroma was irregularly distributed amidst the various epithelial structures and was infiltrated with various amounts of inflammatory cells. In certain cases the tumor showed extensive necrosis, and this was usually associated with a marked inflammatory reaction.

The close similarity in both architectural pattern and secretory activity of the tumor cells to those of the parietal sacculi is striking and at once suggests a genetic relation. We are thus of the opinion that these tumors of the bile duct probably have their origin from the parietal sacculi lying within its wall.

In the great majority of cases carcinoma of the bile duct spreads by direct invasion of the neighboring viscera and the regional lymph nodes. The growth is rarely disseminated to distant organs even in its terminal

phase Early in its course, however, it invades locally and understeps the limits of successful removal The duodenum is generally the first organ to be involved It was involved in 5 cases of the present series in which autopsy was performed Invasion into the duodenum takes place in the deeper layers of its wall, the mucosal surface remaining unaffected as a rule However, when the duodenal mucosa is also part of the tumor process, the clinical features may suggest a primary tumor of the duodenum rather than of the papilla This occurred in 2 cases of

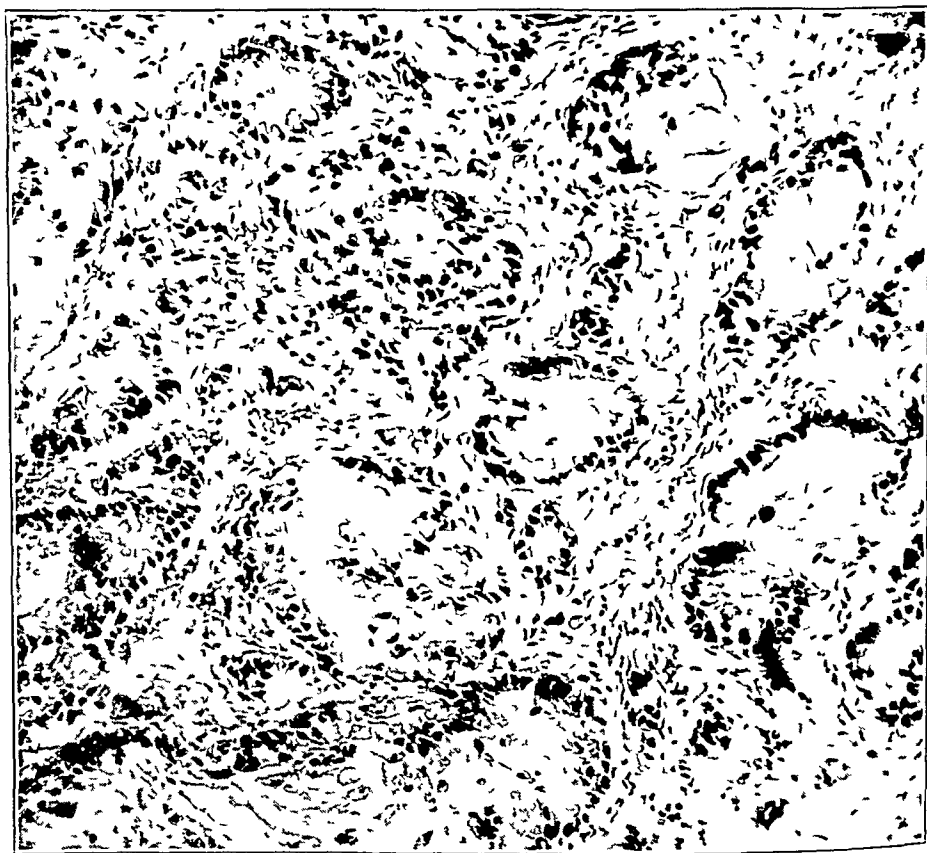


Fig 2—Adenocarcinoma of the terminal portion of the bile duct Note the glandlike structure of the growth and the presence of mucus both within the cells and within the lumens

our series, in each case it was associated with extensive necrosis, ulceration and secondary infection of the duodenal wall

Direct extension of the growth into the pancreas occurred in 2 cases In 1 the duct of Wirsung was obstructed, and this was associated with fat necrosis and a diffuse inflammatory process of the pancreas In another similar obstruction of the pancreatic duct there were multiple abscess formations within the gland

The liver showed evidence of biliary obstruction characterized by biliary and saccular dilatation, round cell infiltration and fibroblastic proliferation

The gallbladder showed particularly interesting changes. In 2 cases it was the seat of an acute suppurative process, and in 4 others it showed evidence of empyema. The mechanism responsible for the lesion in the gallbladder may be explained perhaps on the basis of an ascending infection from the infected tumor in the bile duct and adjoining duodenum. In all likelihood, however, the inflammation of the gallbladder was part of the general cholangitis secondary to biliary obstruction. The nature of this complicated mechanism is of fundamental importance to a proper understanding of the etiology and a proper interpretation of the symptoms of suppurative cholecystitis which complicate obstruction of the biliary duct. When suppuration of the gallbladder occurs it gives rise to clinical symptoms which usually overshadow the primary lesion in the duct. Many patients with carcinoma of the bile duct are first brought to the attention of the surgeon because of the acute fulminating process in the gallbladder, and at operation empyema of the gallbladder is found. Should the patient recover from the operation, he usually succumbs soon after from the effects of the neoplasm in the duct.

The regional lymph nodes are involved about as often as is the duodenum, and their involvement may preclude successful operation in cases in which extirpation of a localized mass might otherwise be contemplated. In this series the regional lymph nodes were involved in only 2 of the cases in which necropsy was done. Distant metastasis is uncommonly observed, even at autopsy. It occurred in none of our cases.

SYMPTOMS

The onset of symptoms was acute in 10 cases and insidious in 7. The earliest treated patient dated the onset of his illness back to three weeks prior to hospitalization, the latest eighteen months, giving an average duration of symptoms of five and two-tenths months. An analysis of the various symptoms showed that jaundice occurred in 16 cases, in 10 of which there was progressive and in 6 of which there was intermittent icterus. Loss of weight occurred in 12 patients, anorexia in 10, vomiting in 5, pain in the right upper quadrant of the abdomen in 7, dyspepsia (i. e., epigastric distress, eructation, flatulence and heart burn) in 9, chills and fever in 4, weakness in 3, intolerance to fat in 2, diarrhea in 1 and fainting and hematemesis in 1. In addition to the aforementioned symptoms, light-colored stools and dark urine were observed by 14 of the patients and tarry stools by 2.

The outstanding physical findings consisted essentially of the following: icterus, 16 cases, dermatitis factitia, 4 cases, purpuric spots, 2

cases, pallor, 2 cases, cachexia, 1 case, malnutrition, 1 case, a large, palpable, firm liver (from 2 fingerbreadths below the costal margin to the level of the umbilicus), 15 cases, hepatic tenderness, 3 cases, general abdominal tenderness, 3 cases, spasm over the upper right quadrant of the abdomen, 2 cases, tenderness and spasm over the gallbladder, 2 cases, distention, 3 cases, and ascites, 1 case

Laboratory studies yielded the following findings. The urine showed the presence of bile in 14 cases. Urobilinogen was absent in 4 cases, tyrosine crystals were present in 1 and no leucine crystals in 1. Amylase was absent in 1.

The icterus index of the blood was elevated in 11 cases, the lowest value was 31.2 and the highest 225, with an average of 112 for the series studied. The van den Bergh test showed a direct immediate positive reaction in 9 cases and a biphasic reaction in 1. The sugar content was elevated in 6 cases, the values ranging from 125 to 174 mg per hundred cubic centimeters of blood. In none of these cases was the patient known to be diabetic. The urea content was elevated in 7 cases, ranging from 19 to 114 mg per hundred cubic centimeters of blood, with an average of 44 mg. The level of cholesterol was elevated to 320 mg per hundred cubic centimeters of serum in 1 case. Moderate secondary anemia was present in 5 cases, and severe secondary anemia, in 2 cases.

Gastric extraction showed hyperacidity and a strongly positive benzidine reaction in 1 case. Duodenal extraction showed absence of bile both before and after the instillation of magnesium sulfate in 3 cases, a 4 plus reaction for bile in 1 case and no amylase in 1 case.

Roentgen examination of the gastrointestinal tract gave negative results in 5 cases, in 2 cases it yielded evidence suggestive of a lesion of the head of the pancreas.

Studies of the gallbladder showed no visualization in 4 cases. In 3 cases an opaque shadow of the gallbladder was seen in a flat roentgenogram.

While in some instances certain features are present with sufficient regularity to be suggestive of the primary lesion in the bile duct, yet because of the lack of any typical symptoms pathognomonic of the disease the diagnosis is not always clear. Such facts, of course, open a field for wide speculation, but it is not our purpose to delve any more into the subject, aside from stating that a correct diagnosis may be made only by careful history taking and by physical and laboratory examinations.

A correct clinical diagnosis of carcinoma of the distal portion of the bile duct was made in 5 of the cases, or 29.7 per cent. In a recent publication by Lieber, Stewart and Lund it was noted that a correct diagnosis was made in only 5.9 per cent of a series of 222 collected cases.

In the remaining 12 cases of our series the following diagnoses were made: cholelithiasis and choledocholithiasis, 2 cases; carcinoma of the head of the pancreas, 4 cases; carcinoma of the stomach with secondary involvement of the bile duct, 2 cases; acute cholecystitis, 2 cases; cholecystitis and cholelithiasis, 1 case; and carcinoma of the gallbladder, 1 case.

Not only is difficulty encountered in making a correct diagnosis on clinical examination of the patient, but often even after intensive exploration of the abdominal organs at the time of operation the true nature of the disease cannot be ascertained. Of 122 operative cases in Lieber, Stewart and Lund's series, an incorrect diagnosis was made at the time of operation in 39. In retrospect, the operative findings in our cases strongly suggest the correct diagnosis. They were overlooked, however, because in each case the main finding at operation pointed to a lesion elsewhere and not to the primary growth in the bile duct. Thus in 4 of the operative cases the lesion noted when the abdomen was opened was empyema of the gallbladder, and the operator, being satisfied as to the patient's ailment, refrained from any further exploration. It has been our experience that even at necropsy a correct diagnosis is not made in many instances until the biliary passages are widely opened and explored.

We wish to cite some of the case reports from our series as examples of the confusing clinical picture which these patients present both to the clinician and to the operator. Of 6 of the operative cases, the lesions in 2 were erroneously diagnosed as empyema of the gallbladder associated with cholangitis and hepatitis, in 2 others they were diagnosed as carcinoma of the head of the pancreas. In these cases they later proved to be carcinoma of the ampulla and papilla of Vater.

REPORT OF CASES

CASE 1—S., a 57-year-old man, was admitted to the hospital complaining of anorexia, pain in the right upper quadrant of the abdomen, jaundice and pruritus of three months' duration. Seven years previously a resection of the ascending colon had been performed for carcinoma. The patient remained well until three months prior to his admission to the hospital, when he first noticed pain in the upper part of the abdomen (especially after partaking of fatty meals), intermittent jaundice and cholelithiasis stools. There was no loss of weight.

Physical examination revealed him to be well developed and well nourished. He was moderately anemic. The right upper quadrant of the abdomen was tender, and the muscles were spastic. The liver was palpable 2 finger-breadths below the costal margin. The carcino-matous was 33; the stool showed absence of bile for ten days, and over the bile reappeared in moderate amounts. The stools showed a strongly positive reaction to benzene. A presumptive diagnosis of obstructive empyema, possibly of malignant origin, was made.

At operation an abscess cavity containing pus was found. The bile ducts were normal on palpation, but the adjoining lymph nodes appeared

enlarged. A cholecystectomy was performed, and the pathologic diagnosis was acute cholecystitis. Three weeks after the operation a biliary fistula developed and a cholangiogram taken through the fistulous opening revealed an obstruction of the papilla (interpreted as a calculus), the bile ducts were dilated. Repeated cholangiograms thereafter showed a distinct round shadow blocking the opening of the papilla. The fistula soon closed, the patient recovered rapidly, bile began to appear in the stools and the jaundice diminished. The patient was then discharged, apparently well. He was readmitted five months later because of the development of painless jaundice associated with clay-colored stools. A gastrointestinal roentgen series was reported normal (fig 3).

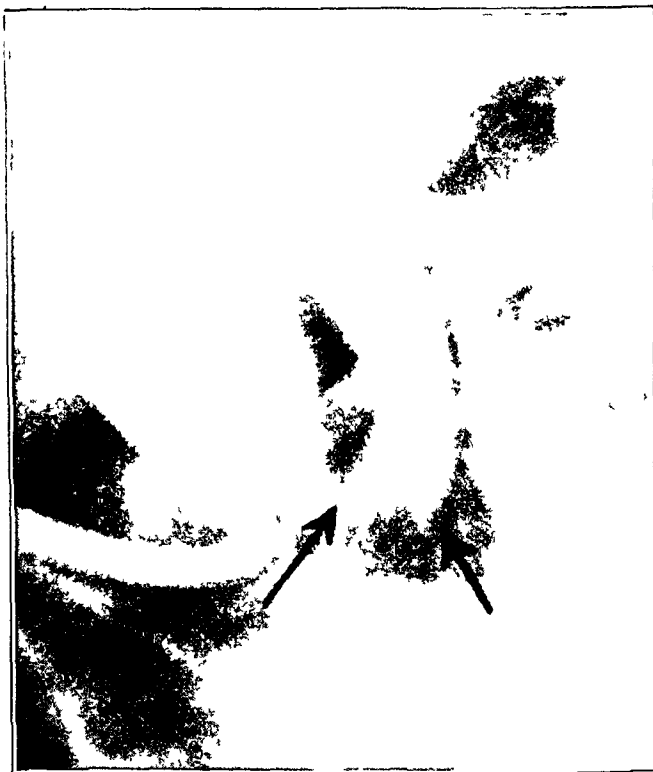


Fig 3—Dilated common bile duct filled with dye. In the papilla is seen a distinct round shadow suggestive of stone formation.

At reoperation the common bile duct was found tremendously dilated. It presented, however, a point of obstruction at the papilla which prevented the passage of a probe. A grating noise similar to that produced by a stone was elicited on attempting to pass the instrument beyond this point. Attempts to recover the supposed stone through an opening in the duct failed. On transduodenal approach to the papilla there was no evidence of stone in the papilla or in the duct. A T tube was then inserted into the common bile duct, and the abdomen was closed. The patient failed to rally from the operation and died six days later.

At autopsy there was found a carcinoma of the papilla with extension to the duodenum. The duodenal mucosa immediately adjoining the papilla was widely ulcerated. There were regional metastases to the lymph nodes and to the pancreas.

The salient features of this case are, first, the acute onset of the disease and the finding of an acutely inflamed gallbladder at the first operation, second, the constant roentgen finding of a round shadow in the papilla, interpreted as representing a calculus, third, the long period between the acute attack of gallbladder disease and cholecystectomy and the appearance of symptoms caused by the papillary neoplasm, and last, the intermittent attacks of jaundice and associated symptoms of biliary obstruction present both before and after operation

CASE 2—H T, a 68 year old man, was admitted to the hospital complaining of loss of weight for two months and icterus and pruritus for two weeks. One year previously he had had pains in the upper part of the abdomen radiating to the back. On physical examination the patient appeared cachectic and jaundiced. The edge of the liver was palpated at the umbilicus, and there was a suggestion of free fluid in the peritoneal cavity. Laboratory examination revealed the icteric index to be 132 and the value for phosphatase 309 units. The van den Bergh test elicited a direct immediate positive reaction. The urine gave a 4 plus reaction for bile. The stools were free of bile and showed a 4 plus reaction to benzidine. There was leukocytosis, with 13,000 white blood cells per cubic millimeter. A preoperative diagnosis of carcinoma of the common bile duct was made. At operation the liver appeared cirrhotic and cholemic and was adherent to the parietal peritoneum. The gallbladder was hidden by adjoining adherent loops of intestine and stomach. When the adhesions were separated and the gallbladder exposed, the latter was found to be thick walled and necrotic, and the cavity was distended with pus. The pancreas and duodenum felt normal. A cholecystostomy was performed, and a section of the gallbladder was removed for biopsy. The pathologic diagnosis was acute and chronic cholecystitis, a culture of the pus recovered from the gallbladder yielded *Staphylococcus aureus* and gram-negative organisms. The patient failed to rally from the operation and died three days later. At necropsy there was found a carcinoma arising from the papilla which extended upward to involve the wall of the bile duct.

Here again it is of interest to note the acute inflammatory process found in the gallbladder at operation, although clinically there were no signs or symptoms to indicate that such a condition existed. Moreover, the carcinoma of the duct was completely overlooked at the time of operation, although clinically there were signs and symptoms to indicate that such a condition existed.

CASE 3—M W, a 48 year old white man, was admitted to the hospital because of icterus, pruritus, paraesthesia and anorexia of two and a half weeks' duration, he had lost considerable weight. On examination, the patient appeared well developed and well nourished. He was icteric, and the skin was covered with scratch marks and purpuric spots. The liver was enlarged and firm, the gallbladder was palpable. The icterus index of the blood ranged up to 105, and the van den Bergh test showed an immediate positive reaction. The stools were free of bile and gave a positive reaction to the benzidine test. A flat plate of the gallbladder showed an opaque shadow, and there was no visualization of the gallbladder with the dye test. A series of gastrointestinal roentgenograms showed an increased duodenal sweep suggestive of tumefaction of the head of the pancreas.

At operation the liver was found enlarged, smooth and cholemic. There was hydrops of the gallbladder, but the lumen was free of stones. The pancreas was the seat of a large, hard mass. A cholecystogastrostomy was performed, and the abdomen was closed. The patient made an uneventful recovery. About sixteen months later he was readmitted to the hospital, because of chills and fever of five weeks' duration. He was markedly icteric, and the liver was enlarged to the level of the umbilicus. He was reoperated on, and the mass in the pancreas was still present. A new cholecystogastrostomy was performed because the stoma of the previous one appeared stenotic. The patient recovered from the operation, and on discharge he was free from symptoms and the icterus had disappeared. He was well for over two years, then he had chills, fever and jaundice at irregular intervals. The stools were frequently black. During the past five weeks he had been vomiting, and he had lost 20 pounds (9.1 Kg) in weight. He was reoperated on, and the mass in the pancreas was still palpable. He died one day after the operation.

At autopsy there was found a carcinoma of the papilla of Vater with metastasis to the duodenum and the pancreas. The gallbladder was the seat of an acute suppurative process, and the pancreas in addition to the metastasis showed chronic pancreatitis.

Of particular interest in this case was the long duration of the growth (three years and eight months) with very little distant metastasis. Equally interesting are the inability of the surgeon to recognize the lesion in the papilla at the time of operation and the constant finding of a mass in the pancreas which was taken to be a carcinomatous growth and the cause of the patient's symptoms.

CASE 4—T. R., a 69 year old man, was admitted to the hospital complaining of recurrent attacks of jaundice, agonizing pains in the right upper quadrant of the abdomen and vomiting. For the past fifteen years he had been subject to attacks of epigastric pains which radiated to the right and to the back. Examination revealed nothing unusual aside from tenderness in the right upper quadrant of the abdomen. The impression was that he was suffering from a stone in the common duct. At operation there was found an acutely inflamed gallbladder containing a large calculus. The common bile duct was dilated and contained pus. A cholecystostomy and a choledochostomy were performed.

He was readmitted fourteen months later, because of jaundice and pruritus. The appetite was good, and there was no loss of weight. On examination he was found to be icteric. The liver was enlarged to 2 fingerbreadths below the costal margin. On reoperation the liver appeared cirrhotic. The common bile duct was dilated to 3 fingerbreadths. At the papilla there was palpated a firm mass the size of a peach stone, although the duct readily permitted the passage of a uterine forceps into the duodenum. A secondary cholecystostomy was performed, but the patient died nine days later.

In this case also the onset of illness was ushered in by an acute inflammation of the gallbladder, which finding was verified at operation. Because of these operative findings, thorough exploration of the duct at the time of the first operation was not done and the growth in the papilla was thus overlooked.

COMMENT

Carcinoma of the bile duct is as a rule a primary lesion and for a long time confines its growth to the duct. As the disease progresses, the growth extends into the muscular wall, but its tendency is to localize in the duct and not to metastasize. In some instances, however, it tends to extend into adjoining structures, especially into the duodenum, in which case it interrupts the muscularis mucosae and continues its course beneath it. When the duodenal mucosa is also involved in the tumor process, ulceration and secondary infection usually follow. These changes are responsible for a host of symptoms not directly related to the ductal growth itself but referable to the changes produced in the duodenal wall. Under such circumstances, for example, bleeding may take place from the ulcerated duodenal mucosa, and blood may appear either in the stools or in the vomitus. Thus, 2 of the patients in this series showed fatty stools which reacted positively to benzidine, and 1 showed gross hematemesis. Involvement of the pancreas, lymph nodes and more distant organs is a rather late occurrence. Metastasis takes place by direct extension and not by the usual route through the lymph or venous channels.

It is of interest to note in this connection that choledocholithiasis is observed to be associated with carcinoma of the bile duct far less commonly than with carcinoma of the gallbladder. In the present series carcinoma of the duct was associated with calculus formation in only 1 case.

In view of the present study of these cases and in correlation of the data with the various theories offered on the histogenesis of carcinoma of the bile duct, we are more inclined to consider these tumors as neoplasms arising from the ductal mucosa or, preferably, from the intramural sacculi of the duct. Throughout the entire series of cases the histologic picture presented by the tumors bore a striking morphologic resemblance to the sacculi described as occurring within the wall of the bile duct. It seems to us, therefore, that these neoplasms may be interpreted in terms of growths arising from this normal glandular structure.

As has been stated, there are no pathognomonic signs and symptoms of early carcinoma of the bile duct. Icterus, loss of weight, asthenia, anemia, anorexia, indigestion and vague abdominal symptoms may occur in various combinations and degrees. Melena is rare, occult blood in the feces is more frequent.

Diagnosis is invariably late, as it is dependent on the onset of symptoms, and it is well recognized that unfortunately the early symptoms of carcinoma of the bile duct are vague and are apt to be confused with those of other lesions of the upper part of the abdomen. There is of necessity a latent period between the earliest carcinomatous formation and the patient's awareness of something amiss, and the duration of

this period cannot be established at present. Owing to the low grade of malignancy of the growth, by the time the disease has produced symptoms of obstruction it is nearing the terminal stage. Early in this presentation the statement was made that the diagnosis of carcinoma of the biliary duct should not present any particular difficulty if the possibility is constantly kept in mind. While this statement holds true in a certain number of cases, exceptions may be made when adjoining organs also become involved. While it is also true that in some instances the signs and symptoms of carcinoma of the duct are rather typical, yet it is in cases presenting atypical features that one is apt to make a diagnostic error unless the condition is suspected and sought for. Among the more frequently encountered diagnostic pitfalls, perhaps empyema of the gallbladder heads the list. In this series, carcinoma of the terminal portion of the common bile duct was associated with an acute inflammatory process of the gallbladder in 6 cases. One can readily conceive the ease with which such a complication will develop if one bears in mind the close anatomic relation which exists between the gallbladder and the rest of the biliary system. It is generally conceded that when stagnation of bile occurs, as it is prone to do in the presence of biliary obstruction, there usually develops general cholangitis, and the gallbladder, being part of the biliary system, is necessarily involved in the inflammatory process. The occurrence of suppuration and empyema formation in the gallbladder is thus easily explained.

In reviewing the cases presented we note several clinical facts. First, in some of the cases of acute involvement the process was ushered in by the classic syndrome of sudden pains in the upper part of the abdomen, radiating to the back, often associated with chills and fever and suggestive of empyema of the gallbladder. In most of the cases these findings were corroborated at operation. Second, a group of cases existed in which there was no clinical evidence of involvement of the gallbladder, yet at operation empyema of the gallbladder was disclosed. Third, there was a group of cases in which the growth in the duct was situated so close to the orifice of the duct of Wirsung as to cause partial or complete obstruction of this duct and set up an inflammatory condition in the pancreas. Under such circumstances the pancreas at the time of operation felt massive and firm and gave the erroneous impression of carcinoma. Last, there was a notable group of ductal carcinomas which produced such extensive metastasis in the duodenum as to overshadow the primary growth in the duct.

Roentgen studies of neoplasms of the terminal portion of the common bile duct have not been fully exploited. The physician's armamentarium has not been exhaustively applied toward the differentiation of this lesion from other closely related diseases. Thus, in our series of 17 patients only 7 were subjected to a routine roentgen investigation

of the gastrointestinal tract for the purpose of ruling out possible malignant disease of this system. No particular attention was paid at the time of examination to any one portion of the intestinal tract. On restudying the roentgenograms for the purpose of this paper it was noted that in 5 of the 7 cases there were either definite or suggestive changes in the second portion of the duodenum. Since carcinoma of this portion of the duct is known to encroach on the lumen of the duodenum and occasionally to ulcerate or stenose this area, it is not startling to find roentgen evidence that such a condition existed. Closer attention to the second portion of the duodenum with this view in mind undoubtedly would yield more illuminating results. It is therefore suggested that in cases of a suspected lesion of the terminal bile duct a routine roentgen examination of the second portion of the duodenum should be carried out.

The prognosis of carcinoma of the bile duct is poor. If the condition is discovered early, resection is indicated. After symptoms of obstruction have developed, anastomosis around the growth, with a lower immediate mortality, is probably better than attempted resection, with a high immediate mortality and with slight chance of cure.

SUMMARY AND CONCLUSIONS

Seventeen cases of primary carcinoma of the terminal portion of the common bile duct with 8 autopsic observations are reported.

In the cases cited in this series, empyema of the gallbladder was frequently associated with this condition.

There are no pathognomonic signs and symptoms characteristic of carcinoma in the terminal portion of the bile duct. The symptoms are readily confused with other, closely allied conditions of the upper part of the abdomen.

Recognition of the pitfalls in the differential diagnosis of this condition and more frequent application of laboratory facilities, especially the roentgen rays, will reduce the high percentage of error in the clinical and operative diagnosis.

SEVERE HEMORRHAGE IN GASTRIC AND IN DUODENAL ULCER

A STUDY OF NINETY CASES

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In the past decade much has been written concerning the treatment of peptic ulcer which shows evidence of gross bleeding. During this period many physicians and surgeons have come to respect bleeding as a major complication of ulcer but as yet no uniformly accepted method of treatment has been established. Recently Meulengracht¹ published a report on a group of cases of bleeding peptic ulcer in which remarkably good results were obtained by treatment with a full puree diet. His conclusions favor a passive attitude toward this complication, and it is natural that physicians should welcome so simple a method of managing a condition which, with a great variety of treatments, has a mortality reported as ranging from 1 to 35 per cent.

This paper is an analysis of the observations on a group of 90 patients with bleeding ulcer. In general, these observations lead one to believe that a large percentage of patients with bleeding ulcers should be treated actively and at an early stage by surgical measures if a high mortality is to be avoided. It is evident from a study of these cases that up to the present time a definite program of treatment has not been followed, rather, the therapy has been determined by clinical examination of the individual patient. As a result of the findings in this group of patients, however, therapeutic measures have been formulated which, it is hoped, will help to improve results.

Complications of peptic ulcer apparently are becoming more rather than less frequent, in spite of increasing knowledge of the pathologic picture of this disease. Hemorrhage is by far the most frequent major complication, occurring in approximately one fourth of all cases, and except for perforation it is the most disturbing. Proper treatment rests on accurate diagnosis, knowledge of the pathologic picture, an appreciation of the value of the available methods of treatment and, when operative intervention is indicated, competent surgical handling.

From the Department of Surgery, the New York Hospital, and Cornell University Medical College.

¹ Meulengracht, E. Behandlung von Hamatemesis und Melana mit unen-
geschränkter Kost, *Wien klin Wchnschr* 49 1481, 1936.

DIAGNOSIS

The commonest cause of bleeding from the stomach or duodenum is peptic ulcer, and this diagnosis can usually be made after such other possible causes as esophageal varices, cancer and the hemorrhagic diatheses have been excluded. Except with a small group of patients who have had absolutely no antecedent history of pain or indigestion, it is practically impossible to say whether the bleeding comes from an acute or a chronic ulcer.

TABLE 1—*Comparative Incidence of Acute and Chronic Ulcers Associated with Hemorrhage*

Author*	Cases of Acute Ulcer	Cases of Chronic Ulcer
Bulmer	15	23
Burger and Hartfall	15	30
Chiesman	13	17
Hellier	2	28
Nielsen ¹⁴	16	39
Holman (New York Hospital series, this paper)	0	26
Total	61 (27%)	163 (73%)

* References in this and in the following tables not accompanied by superior figures will be found in the following list

- Aitken, R. S. The Treatment of Profuse Bleeding from the Stomach and Duodenum, *Lancet* **1**: 839, 1934
- Armstrong, G. C. The Wisdom of Surgical Interference in Hematemesis and Melena from Gastric and Duodenal Ulcer, *Brit. M. J.* **2**: 1087, 1899
- Babey, A. M., and Hurst, A. F. The Incidence, Mortality and Treatment of Hemorrhage in Gastric, Duodenal and Anastomotic Ulcer, *Guy's Hosp. Rep.* **86**: 129, 1936
- Bulmer, E. The Mortality from Hematemesis: Analysis of Five Hundred and Twenty Six Cases, *Lancet* **2**: 168, 1927, Mortality from Hematemesis: Supplementary Analysis *ibid.* **2**: 720, 1932
- Burger, G., and Hartfall, S. G. Hematemesis in Peptic Ulcer, *Guy's Hosp. Rep.* **84**: 197, 1934
- Chiesman, W. E. Mortality of Severe Hemorrhage from Peptic Ulcers, *Lancet* **2**: 722, 1932
- Conybeare, J. J. Prognosis of Gastric and Duodenal Ulcer, *Lancet* **2**: 1017, 1935
- Davies, T. A. L., and Nevill, R. W. Prognosis of Hematemesis: Statistical Review, *Brit. M. J.* **2**: 858, 1934
- Finsterer, H. Operative Treatment of Severe Gastric Hemorrhage of Ulcer Origin, *Lancet* **2**: 303, 1936
- Fowler, W. M., and Hurevitz, H. M. Bleeding Peptic Ulcer, *J. Iowa M. Soc.* **25**: 115, 1935
- Hellier, F. F. Etiology and Mortality of Hematemesis, *Lancet* **2**: 1271, 1934
- Hinton, J. W. Massive Hemorrhage in Peptic Ulcer, *Ann. Surg.* **101**: 856, 1935
- Umber, F. Zur Prognose und Behandlung grosser Ulcusblutungen, *Deutsche med. Wchnschr.* **2**: 1265, 1935

PATHOLOGIC PICTURE

While opinion regarding individual cases may vary, ulcers are commonly classified as either acute or chronic, depending on the pathologic findings, including the extent to which the walls of the viscus have been penetrated. As a rule, an acute ulcer remains superficial and does not penetrate the muscular layer of the stomach or duodenum, and for this reason it is not likely to be the source of severe bleeding. The greater incidence of hemorrhage in chronic ulcers is reflected in table 1, in which a group of cases observed at operation or at necropsy is listed.

Unfortunately, the nature of the pathologic change in a bleeding ulcer cannot be determined by its clinical manifestations. The important

question as far as treatment is concerned is whether a single bleeding point can be easily found at operation. Objection is sometimes raised to operation on the ground that the hematemeses may be caused by a capillary oozing from a diffusely congested mucosa, an idea popularized by White² in 1901. However, Bortz³ in 1932, after a thorough search of the literature, could find only 52 cases in which this occurred, and in table 2 it will be seen that in all but a few of the 472 collected cases the source of the hemorrhage was readily established. In the great majority it was a large, eroded vessel in the base of the ulcer.

Eight of the fatal ulcers in this series showed such a large eroded vessel—the pancreaticoduodenal artery in 7 cases and the superior mesenteric artery in 1. These vessels protruded at the base of the ulcer.

TABLE 2—*Identification of Bleeding Point*

Author*	Autopsy	Operation	Total	Source of Bleeding Not Demonstrable
Aitken	10	21	31	2 (at operation)
Allen and Benedict ⁶	8		8	0
Armstrong	9		9	0
Bulmer	38		38	0
Burger and Hartfall	30		30	0
Chiesman	45		45	1
Christiansen ⁷	16		16	0
Finsterer		112	112	0
Fowler and Huevitz	11		11	1
Hellier	30		30	0
Hinton	8	21	29	1 (at autopsy)
Nielsen ¹⁴	55		55	0
Umber		29	29	1
Holman (New York Hospital series, this paper)	6	23	29	0
			472	

* References in this table not accompanied by superior figures will be found in the list appended to table 1.

through dense scar tissue, which precluded any retraction. Moreover, in several cases the vessels contained partially digested clots—the usual finding, according to Hunter.⁴

The location of the ulcer also plays an important role with respect to the occurrence of serious hemorrhage. Ulcers on the anterior wall of the duodenum rarely lead to dangerous hemorrhage, since there are no large vessels in this region, ulcers of the posterior wall possess the greatest capacity for serious or fatal hemorrhage because of their proximity to the superior and inferior pancreaticoduodenal arteries.

2 White, W. H. Are Not Some Patients Said to Be Afflicted with Gastric Ulcer Really Suffering from a Different Disease? *Lancet* 1 1819, 1901, Discussion on Hematemesis, *ibid* 1 1470, 1906.

3 Bortz, E. L. Diffuse Hemorrhage from Stomach, *Arch. Int. Med.* 50 (July) 1932.

4 Hunter, J. B. Action of Saliva and Gastric Juice on Clotting Blood, *Brit. J. Surg.* 16 203, 1928.

These most intractable ulcers penetrate the pancreas, become calloused and erode into the large vessels, which are in direct contact with the posterior wall of the duodenum

Contrary to the experience in European clinics, it appears that in the United States gastric ulcers are much less likely to be the source of fatal hemorrhage than are duodenal ulcers, but because of the vascularity of the stomach serious hemorrhage is always possible

Most jejunal and marginal ulcers bleed to some extent, and occasionally, but not so frequently as with duodenal or gastric ulcer, the bleeding is fatal. Thus, Wright⁵ reported 7 deaths in 124 cases of bleeding marginal or jejunal ulcer

MORTALITY

Since one possible reason for the wide variation of published statistics on the prognosis and the mortality of bleeding peptic ulcer is the difference in the types of patients included, it should be stressed that this series includes only patients who were admitted to the hospital because of severe hemorrhage (hematemesis or melena or both) and who were proved beyond any reasonable doubt to be bleeding from a peptic ulcer. It consists of patients who were personally examined at the time of bleeding or who were interrogated at some later date to confirm opinions or data in the charts, as well as patients who came to necropsy. Finally, it is made up of the class of patients seen in a general ward service. The statistics of Hurst⁶ support the impression that the class of patients seen in private practice is not so frequently subject to the severe complications of perforation and hemorrhage as that seen in charity practice.

Of the 90 patients, 12 (13.4 per cent) died in the hospital from hemorrhage. As is shown in table 3, this approximates the average mortality for cases reported from other clinics.

In table 4 the 12 fatal cases are summarized. Four of the 12 patients who died were never in a condition that warranted operative intervention. One of these was admitted to the medical service because of mental confusion and hemiplegia resulting from a cerebral accident. Seventeen days after admission symptoms of internal hemorrhage suddenly developed, and the patient died within twenty-four hours. Autopsy revealed a large, indurated duodenal ulcer. A second patient was admitted to the medical service in shock and died within twelve hours without hematemesis or melena, at autopsy a large, eroded pancreaticoduodenal artery was found in the base of a duodenal ulcer. A third patient, with

⁵ Wright, G. Collective Inquiry into Gastro-Jejunal Ulceration, *Brit J Surg* 22 433, 1935

⁶ Hurst, A. F. The Incidence, Mortality and Treatment of Hemorrhage, *Guy's Hosp Rep* 86 135, 1936

amyotrophic lateral sclerosis and vague epigastric pain, was given a gastrointestinal roentgen examination. He subsequently showed signs of internal bleeding and in spite of repeated transfusions never recovered from the shock caused by the bleeding and died in thirty-six hours. A fourth patient entered the hospital after severe repeated hematemesis at home for three days. He had hyperpyrexia, became comatose twelve hours after admission and died within fifty hours. Four patients died after operative procedures undertaken with the hope of controlling hemorrhage and thereby averting a fatal outcome. Four died from hemorrhages that might have been controlled if operation had been performed. In spite of their acute loss of blood and anemia, in the case of each of the 4 there was a period after the initial hemorrhage when the patient's condition was sufficiently satisfactory to warrant operative intervention.

TABLE 3—Mortality

Author*	Number of Cases	Deaths	Mortality, Percentage
Aitken	255	27	11
Allen and Benedict ⁹	138	20	14.5
Babey and Hurst	82	4	5
Burger and Hartall	157	31	22.5
Chiesman	191	48	25
Conybeare†	600	22	3.7
Christiansen ⁷	289	23	7.9
Davies and Nevill	391		21
Fowler and Hurevitz	72	17	23
Hellier	202	30	14.8
Meulengracht ¹	273	3	1
Umber	433	41	9.5
Holman (New York Hospital series, this paper)	90	12	13.4

* References in this table not accompanied by superior figures will be found in the list appended to table 1.

† Conybeare stated that the mortality from hemorrhage in chronic ulcers is between 5 and 10 per cent.

With 1 exception, all the patients who died had hematemesis. The average time between the onset of bleeding and the death of the patient was eight days, but it should be emphasized that 6 patients died within four days. Christiansen⁷ noted that in his experience and in the experience of others (Meulengracht,¹ Wood,⁸ Allen and Benedict⁹) the average duration of bleeding before death was between thirteen and sixteen days, he concluded that the majority of patients die from some complication of hemorrhage rather than from the loss of blood itself. All the 8 patients not operated on in the present group died as a direct result of bleeding. In 2 of those who died the first and only hemorrhage

7 Christiansen, T. On Massive Hemorrhage in Peptic Ulcer, *Acta med Scandinav* **84** 374, 1935, Uremia as Cause of Death in Massive Hemorrhage from Peptic Ulcer, *ibid* **85** 333, 1935.

8 Wood, I. J. Treatment of Hemorrhage, *Brit M J* **2** 115, 1936.

9 Allen, A. W., and Benedict, E. B. Acute Massive Hemorrhage from Duodenal Ulcer, *Ann Surg* **98** 756, 1933.

TABLE 4—*Analysis of Deaths (New York Hospital Series)*

Patient	Age	Type of Bleeding	Number of Hemorrhages	Operation	Interval between Onset of Bleeding and Operation	Condition	Cause of Death	Post operative Duration of Life	Bleeding Point	Autopsy	Comment
B	27	Melena and hematemesis	1	Suture of bleeding point	20 days	Poor	Pneumonia	2 days	Posterior duodenal ulcer	+	
S	34	Melena and hematemesis	5	Exploratory laparotomy	12 days	Poor	Bleeding	36 hr	Jejunum ulcer	+	Bleeding continued from one unidentified jejunal ulcer 3 jejunal ulcers present
F	41	Melena and hematemesis	1	Gastric resection	17 days	Poor	Pneumonia	4 days	Posterior duodenal ulcer	0	Bleeding continued in hospital
I	63	Melena and hematemesis	1	Gastric resection	7 days	Poor	Shock	17 hr	Gastric ulcer	0	
W	47	Melena and hematemesis	3	Gastric resection	0	Poor	Bleeding	7 days	Jejunum ulcer	+	
R	51	Hematemesis	1	0	0	Poor	Bleeding	6 days	Duodenal ulcer	0	
D	59	Melena	1	0	0	Poor	Bleeding	60 hr	Posterior duodenal ulcer	+	
S	63	Melena and hematemesis	1	0	0	Poor	Bleeding	36 hr	Posterior duodenal ulcer	+	
U	23	Melena and hematemesis	1	0	0	Poor	Bleeding	24 hr	Posterior duodenal ulcer	+	
C	34	None	1	0	0	Poor	Bleeding	5 days	Posterior duodenal ulcer	+	
L	40	Melena and hematemesis	2	0	0	Poor	Bleeding	4 days	Posterior duodenal ulcer	+	
G	43	Melena and hematemesis	1	0	0	Poor	Bleeding (uremia)	4 days	Posterior duodenal ulcer	0	

* All patients listed in this table were men
† On duration of life after onset of bleeding

followed immediately on completion of a barium roentgen study of the stomach and duodenum. It should, perhaps, be pointed out again that all the ulcers were chronic and that in all those examined at operation or necropsy a definite bleeding point was found, which usually was a branch of the pancreaticoduodenal artery in the base of a duodenal ulcer.

PROGNOSIS

Of all the factors to be considered in the prognosis of hemorrhage from ulcer, the patient's sex and age, the continuation or repetition of bleeding after hospitalization and the onset of bleeding while the patient is under strict medical care seem to be the most important.

In this group of patients only 19, or about 22 per cent, were women, none of whom died.¹⁰ Most observers agreed that hemorrhage in young

TABLE 5—Mortality in Various Age Groups

Author*	Age Groups							
	1-29 Years		30-39 Years		40-49 Years		50+ Years	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Allen and Benedict ⁹	19	1	31	1	33	2	55	16
Bulmer	218	14	101	11	94	14	44	14
Burger and Hartfall	24	2	27	3	37	13	49	13
Hellier	37	6	45	4	61	7	59	13
Hinton	14	0	18	3	12	3	8	4
Meulengracht ¹	20	0	48	0	57	2	81	1
Holman (New York Hospital series, this paper)	10	2	20	2	30	3	30	5
Total	372	25	290	24	324	44	326	66
Mortality percentage	6.7		8.2		13.6		20	

* References in this table not accompanied by superior figures will be found in the list appended to table 1.

women rarely leads to death and the mortality is estimated at about 1 per cent.

The average age of the patients who recovered from the hemorrhage was 41 years and of those who died was 45.5 years—not so striking a difference as that found by Allen and Benedict,⁹ who gave the respective average ages as 41.8 and 56.3. In table 5 a group of patients is analyzed to show the increasing mortality with advancing years. The higher mortality in the older groups is probably due to their greater susceptibility to complications as a result of loss of blood and also (in certain patients with arteriosclerosis) to loss of elasticity of the walls of the vessels. However, this increased mortality among the older patients has no relation to the chronicity of the ulcer, since the average duration of symptoms in the group who recovered was four and two-tenths years,

10 Since the writing of this paper a 67 year old woman has died from hemorrhage of a duodenal ulcer which had eroded the pancreaticoduodenal artery.

in contrast to four years in the group who died. In 1 patient who died the hemorrhage was the first indication of his disease, although autopsy revealed a chronic penetrating ulcer in the posterior wall of the duodenum.

The third prognostic indication, a very important one, is the continuation or immediate recurrence of bleeding after the patient has been hospitalized and treated for twenty-four to forty-eight hours. Table 6 illustrates the gravity of such uncontrolled bleeding.

Finally, of particular interest in the group of patients who died were 4 in whom hemorrhage occurred while they were receiving medical care for their ulcers in the hospital. In contrast, not one of the 78 patients who recovered had spontaneous hemorrhage while in bed in the hospital. Such a hemorrhage is a comparatively rare complication, and Hurst⁶ stated that he has never witnessed it in a patient receiving strict

TABLE 6—*Mortality in Relation to Response to Treatment*

Author*	Mortality After Satisfactory Immediate Response to Medical Treatment, Percentage	Mortality After Unsatisfactory Immediate Response to Medical Treatment with Continuation or Immediate Repetition of Bleeding, Percentage
Babey and Hurst	0	27
Burger and Hartfall	8.5	33
Ohlesman	1.6	74
Davies and Nevin †	9.8	52.8
Holman (New York Hospital series this paper)	6.4	46

* References in this table not accompanied by superior figures will be found in the list appended to table 1.

† Hematemesis from any cause.

medical therapy. As might be expected, all 4 patients had a chronic ulcer, and the 3 on whom necropsy was performed had large, gaping arteries in the base of the ulcer. The fourth patient had had a gastrocolic fistula repaired with a dismantling of the gastroenterostomy six months previously, and at that time a chronic duodenal ulcer was present.

As has been suggested by Ingegnò,¹¹ studies of the blood urea may aid in the prognosis and also in determination of the degree of hemorrhage. Wood⁸ found that a rising value for blood urea or a value above 80 mg per hundred cubic centimeters is a sign of poor prognosis, although wide variations occasionally occur in a bleeding patient. In 2 patients in this series the values for blood urea were found to be high and to increase as the condition grew worse. Both patients died in a state similar to uremic coma.

11 Ingegnò, A. P. The Elevated Blood Urea of Acute Gastrointestinal Hemorrhage and Its Significance, *Am J M Sc* 190:770, 1935.

THERAPY

Although most patients with bleeding ulcers should be given an opportunity to recover under conservative treatment, continued gross bleeding is more and more widely accepted as requiring surgical therapy. The specific indications for immediate surgical intervention are (1) continuous or repeated hemorrhage and (2) primary hemorrhage after the patient has been completely at rest in the hospital. Not only is the mortality in this class of patients (table 5) very high under conservative therapy (approximately 50 per cent), but in every patient in this series whose ulcer was visualized either at operation or at necropsy the bleeding vessel was so large that it is doubtful whether anything short of a direct attack on it could have controlled the hemorrhage.

Resection, when feasible, is the ideal procedure, and in this series no patient has had a recurrence of bleeding after such an operation. However, because of the patient's condition less formidable operations often are employed. It would seem wise always to make a direct attack on the bleeding point, although ligation of the vessels that lead to the ulcer occasionally is a successful alternative (von Haberer,¹² Allen and Benedict⁹). Gastroenterostomy should be performed only if obstruction is present, and control of the bleeding point should be attempted at the same time. In this series gastroenterostomies were performed on 4 patients because of bleeding coincident with obstruction, and all have remained perfectly well. Of 5 patients without obstruction, 2 have had recurrent hemorrhage after gastroenterostomy, a finding that coincides with the experience of others (Westermann,¹³ Nielsen,¹⁴ Ryle¹⁵).

Large amounts of blood should be available for transfusion during operation and particularly after control of the bleeding point. As much as 1 or 2 liters of blood should be given at this time, and as much again can be safely administered within the next twenty-four hours. When this regimen is followed, there need be little danger of a fatal outcome during or shortly after the operation. Postoperatively, careful feeding is essential, and vitamins should be given parenterally to patients whose diet has been deficient.

In this series of 90 patients, 24 were operated on: 8 during active bleeding, with 4 deaths, and 16 within four to six weeks after hemorrhage, without a death—a combined mortality of 16 per cent. All 4 patients who died after operation had failed to respond to a protracted

12 von Haberer, H. Chirurgische Behandlung des Magen- und Duodenalgeschwüres, München med Wchnschr **80** 1577, 1933.

13 Westermann, J. J. Surgical Aspects of Bleeding Gastric and Duodenal Ulcers, *Ann Surg* **101** 1377, 1935.

14 Nielsen, N. A. About the Choice Between Medical and Surgical Treatment of Ulcus Ventriculi and Duodeni, *Acta chir Scandinav* **55** 57, 1923.

15 Ryle, J. A. Failures of Gastric Surgery, *Lancet* **1** 890, 1934.

conservative regimen and when finally operated on as a last resort were extremely poor operative risks. Two of these died from pneumonia two days and four days respectively after gastric resection. One patient with several bleeding jejunal ulcers died from a continuation of the bleeding from one of the ulcers, which had not been found at the time of the operation. These deaths might have been avoided had the patients been operated on earlier, when they were in better condition. Patients rarely succumb during the operative procedure, and complications, such as pneumonia, peritonitis and uremia, are responsible for the great majority of postoperative deaths.

Of the 90 patients whose cases are reported here, some form of gastric operation had been done in the remote past on 22. Gastroenterostomy had been performed on 15, resection on 1 and simple closure of a perforated ulcer, pyloroplasty or a dismantling procedure on the remaining 6. Twelve of these 22 had never bled until after their initial operation, performed for the treatment of an uncomplicated ulcer. It would seem, therefore, that operation—particularly gastroenterostomy—performed on patients with ulcers that have never bled need not be expected to prevent future bleeding unless in the course of the operation the source of bleeding is eliminated.

Patients with ulcer who are admitted for symptoms other than bleeding but who give a history of hemorrhage in the past should be treated as are patients with uncomplicated ulcer. My experience, however, and that of others indicate that without surgical intervention which eliminates the ulcer the subsequent course is often unsatisfactory from the standpoint of both pain and tendency to recurrence of bleeding. Thus, 28 of 69 patients (40 per cent) followed after discharge from the hospital have shown unsatisfactory results, a figure that approximates the findings of Allen and Benedict⁹ and those of Westermann.¹³ Jordan and Kiefer¹⁰ found that 70 per cent of patients who had had two or more hemorrhages were doomed to suffer another. When surgical therapy is undertaken for these patients, gastric resection is advisable, since this operation offers the best protection against future hemorrhage.

SUMMARY AND CONCLUSIONS

A review of the cases of 90 patients with serious hemorrhage from peptic ulcer is presented.

In over 98 per cent of patients subjected to operation or examined post mortem the bleeding point was easily located, and in most a large eroded vessel could be demonstrated.

16 Jordan, S. M., and Kiefer, E. D. Complications of Peptic Ulcer. Their Prognostic Significance, *J. A. M. A.* **103** 2004 (Dec. 29) 1934.

The most important factors in the mortality are age, sex, immediate recurrence of bleeding after complete rest and onset of bleeding under a strict medical regimen

Early operation is usually advisable for men over 40 years of age who have immediately recurrent or persistent bleeding after complete rest in bed. Operation is even more urgently indicated for patients who begin to bleed while at complete rest under a medical regimen.

Surgical procedures should not be used as a prophylactic measure against future bleeding for patients who have never bled.

Patients with a history of bleeding in the distant past should be treated similarly to those with uncomplicated ulcer. However, conservative treatment of patients with a past history of bleeding is unsatisfactory in from 40 to 70 per cent of cases.

Notices

SYMPOSIUM ON PERIPHERAL VASCULAR DISEASES

A symposium on peripheral vascular diseases, comprising at least eleven papers and an editorial, will be published in the February issue. The papers now scheduled have been written by Drs Frank V. Theis and M. R. Freeland, Chicago; Alton Ochsner and Michael DeBakey, New Orleans; John Homans, Boston; Geza de Takats and John C. Reynolds, Chicago; Irving S. Wright, New York; C. A. Moyer and W. G. Maddock, Ann Arbor, Mich.; R. H. Smithwick, Boston; Gordon Murray, Toronto, Canada; Louis G. Herrmann and Edward J. McGrath, Cincinnati; Walter F. Kvale, Lucian A. Smith and Edgar V. Allen, Rochester, Minn.; and Leland S. McKittrick, Boston. The symposium has been compiled under the direction of Dr. Arthur W. Allen, Boston.

Editorial

PERIPHERAL VASCULAR DISEASE

During the past decade there has been widespread interest in disorders of the peripheral circulation. This has led to the establishment of special clinics for the study and treatment of these conditions in a large number of medical centers in the United States. In spite of the continued lack of accurate knowledge of the underlying causes, much has been learned regarding the care of patients suffering from inadequate arterial flow to the extremities. Most of the disorders resulting from this condition have certain common characteristics, and the same general principles of management can be applied to them. Although the types of disability encountered in patients suffering from peripheral lesions associated with diseased veins are different in many respects from those encountered in patients with narrowed arteries, their management has usually been taken over by the special clinics interested in the whole problem of peripheral circulation. Concentrated interest in such conditions has varied considerably in different localities as regards the departments of general medicine concerned. Internists, surgeons and various specialists under these main divisions have all played their part. Research has been carried out by a wide variety of investigators. This has resulted in a better understanding of the situation, with marked influence on the proper care of the patient.

Practitioners have become cognizant of the need of palpating the peripheral vessels in the lower extremities of patients whose complaints indicate the possibility of inadequacy of circulation. They have a better idea concerning the interpretation of their findings in this respect and can frequently classify the lesion if one is present. It has been learned that certain general measures of study and treatment apply to a large group of peripheral vascular disorders. The effect of associated generalized diseases, such as arteriosclerosis, and of diabetes on the vascular tree are more accurately interpreted. The influence of the sympathetic nervous system on the nutrition of the distal parts of the extremities is now recognized, although the mechanism of its irregularity is not often apparent.

Many remedies in the form of vasodilators and mechanical devices have been the natural development in this field. To a large degree these have proved disappointing, but under certain circumstances they have some merit. Since nearly any disease is improved under the detailed, special care of those particularly interested in a successful

outcome, one must be on one's guard against attributing improvement to a specific measure rather than to the natural effect of rest, position, hygiene, proper food, exercises and the elimination of harmful influences. For these reasons it is informative to withhold specific measures of treatment in many cases until a proper evaluation of the situation can be made. This often requires from one to two weeks of care and study in the hospital, especially for patients suffering from arteriosclerotic obliterative disease and thromboangitis obliterans.

In the arrangement of the symposium presented in this issue an attempt is made to cover as many of the phases of the problem as space permits. Many authorities who could have contributed much to the subject were, of necessity, not solicited. It is realized that for this reason the review may appear inadequate. It is intended to present some of the general principles as they are understood today and various research approaches that are being made in different localities in America.

ARTHUR W. ALLEN, M.D.

CONSERVATIVE TREATMENT OF OCCLUSIVE ARTERIAL DISEASE

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NEW YORK

The steady increase in the number of clinics where internists and surgeons are cooperating closely in an attempt to solve the many problems associated with peripheral vascular diseases constitutes an encouraging index of the care which patients suffering from these conditions will receive in the future.

Although the object of all internists and surgeons may be conceded to be the ultimate benefit of the patient and his restoration to a life as nearly normal as possible, the training of the two groups tends toward different philosophic and technical approaches to this objective. This gulf is widened by isolation and narrowed by close association. The problems involved will receive sounder consideration as a result of continuous interplay of surgical and medical opinion, and no clinic devoted to this field can be considered adequate which does not make this inevitable.

In general, medical care of the extreme forms (ulceration and gangrene) of vascular disease rests on conservative therapy, i. e., on allowing epithelization or self amputation to take place. Surgical care has been directed toward quick healing and, this failing, toward some radical procedure, such as amputation or ganglionectomy. Obviously, in instances of infection which spreads rapidly in spite of attempts to control it and which shows evidence of toxic absorption and sepsis, most workers will agree that amputation is the logical recourse. When the lesion is chronic rather than acute the problem is more equivocal. The surgeons call attention to the long period of inactivity of the patient and the economic loss involved in maintaining a conservative regimen for a period varying from three to eight or nine months, when with amputation the period could be reduced to six weeks of hospitalization. They point out also that many patients fail to get better despite conservative therapy, and are eventually treated by amputation. The internists, on the other hand, ask whether most patients would not

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prefer to wait a few extra months for preservation of an extremity, even an imperfect one. They ask also how many months must elapse after the patient leaves the hospital before he is able to get about and especially before he is able to use an artificial limb. What, they ask, of the 40 to 60 per cent of arteriosclerotic patients who, having had an amputation, never learn to use an artificial limb? These questions must be considered with each patient in relation to many additional factors, including the type and extent of the disease, the age of the patient, the potential capacity for future activity, the associated pain, the course and complications of the disease and the results of clinical laboratory and roentgen studies. In the ideal service these factors are reviewed jointly by the medical and the surgical group in an endeavor to determine the proper course to pursue.

If conservative therapy is selected for a patient with occlusive arterial disease, the choice of methods is wide, this indicates that, although several may be worth while, there is no specific cure. The immediate object of the various forms of treatment is improvement of the circulation to the involved area by vasodilation of the active vessels, widening of the collateral channels and reestablishment of canals through old occluded vessels. An endeavor will be made to describe such procedures as seem to warrant discussion, with an attempt at evaluation of each in the light of the experience obtained at the clinic for vascular disease of the New York Post-Graduate Medical School and Hospital and the experience of reliable workers elsewhere as described in their published reports or in personal communications. It should be recognized that knowledge in this relatively newly explored field is in a state of flux and that any such attempt at evaluation is curbed by difficulties. The apparent truth of today may be the error of tomorrow.

Since the most important occlusive vascular diseases are arteriosclerosis obliterans and thromboangitis obliterans and since much of the present day therapy has been used for both, my discussion will apply chiefly to these conditions, specific applications being pointed out when indicated.

REST

Whenever there is ulceration, gangrene, marked progressive discoloration, pronounced and sudden local coldness or severe "rest pain," the involved extremity should be placed at relative rest. The level selected for maintenance of the most satisfactory circulation possible under the circumstances has been shown by Reid¹ to be very important. If the extremity is kept in a dependent position for too long, the veins become engorged, and the engorgement results in increased

¹ Reid, N. R. A General Consideration of Blood Supply in the Practice of Medicine and Surgery, *South M. J.* **26** 107 (Feb.) 1933.

venous and capillary pressure and stagnation of blood. If, on the other hand, the extremity is kept elevated, it becomes blanched and bloodless in appearance and the tissues become ischemic, since the force within the diseased arteries is usually insufficient to carry fresh blood to the tips of the extremity. Such elevation, when prolonged, has been a frequent cause of amputation in the past.

Between these extremes is a level which appears to be the most efficient from the standpoint of proper blood supply. This is the point at which the superficial veins fill to such an extent that they project slightly above the level of the skin. It will usually be found from 3 to 6 inches (7.5 to 15 cm.) below the level of the heart. At this level gravity assists the flow of arterial blood into the limb, and the blood is not retarded in its return by too greatly increased venous back pressure.

Rest should be continued until the lesion is healed or the acute episode is completely over, after which activity should be undertaken guardedly and under observation until the return of the condition is considered unlikely. Specific vascular exercises should be the only exceptions to this.

ACTIVE VASCULAR EXERCISES

1 *Buerger's Exercises*—Various slight modifications of the exercises described by Buerger² have been accepted and used widely to exercise the vascular tree, to clear away stagnant blood and to stimulate the opening of the collateral vessels. A suggested technic is as follows. The patient rests on his back in bed. An incline beginning at the level of the hips is built up on the foot of the bed. The angle of inclination should be 45 to 60 degrees. Pillows or the back of an inverted chair may be used. The legs are (a) elevated on this incline for one to three minutes, (b) lowered over the edge of the bed for three to ten minutes and (c) rested at bed level (horizontally) for five to ten minutes. This cycle is repeated five or ten times twice or three times a day. Color changes (blanching on elevation and rubor on dependency) clearly indicate that blood is draining from and filling the vascular tree. The timing should be such that neither blanching nor rubor is marked for more than one minute.

2 *Allen's Exercises*—Allen³ has suggested a modification of this procedure which is helpful if the feet are not too painful. While the legs are hanging over the edge of the bed, further exercises are performed as follows: (a) The feet are extended downward, (b) the feet are raised by flexion at the ankle joint, not by raising the legs, (c)

2 Buerger, L. *The Circulatory Disturbances of the Extremities*, Philadelphia, W. B. Saunders Company, 1924.

3 Allen, A. Recent Advances in the Treatment of Circulatory Disturbances of the Extremities, *Ann Surg* 92:931 (Nov.) 1930.

the toes are turned inward as far as possible, (d) the toes are turned outward as far as possible, (e) the toes are spread with the feet in normal position, and (f) the toes are "closed". This should be repeated during the dependent phase of each cycle.

CARE OF THE EXTREMITIES

Once the diagnosis is made, whether an acute condition is present or not, meticulous care must be taken of the extremities involved. If free from open lesions they should be washed carefully at least three times a week with warm (not with hot) water and rubbed thoroughly thereafter with olive oil or hydrous wool fat to keep the skin soft. Corns and calluses should be carefully softened with salicylic acid ointment. Paring should be discouraged except in the most expert hands. The nails should be cleansed and pared with extreme care to avoid production of minor lesions requiring surgical treatment. Trauma and frostbite must be avoided. Shoes must be soft and must fit well, to avoid abrasion. Socks should be of soft wool, to cushion the feet.

ABSTINENCE FROM TOBACCO

It is now generally recognized that the use of tobacco in the presence of impaired circulation is inadvisable. It was first noticed by Silbert⁴ (among others) that in cases of thromboangitis obliterans smoking is a markedly aggravating, if not the most important etiologic factor. Most clinics subscribe to this theory, at least in reference to aggravation. Experimental studies by Maddock and Collier,⁵ Barker,⁶ Wright and Moffat⁷ and Lampson⁸ have established the fact that the smoking of tobacco usually produces diminution of the blood supply to an extremity, normal or otherwise by constriction of the peripheral arterioles, as determined by thermocouple readings and by capillary microscopic and plethysmographic studies. That this is not due to deep respiration as has been claimed by Mulinos and Shulman⁹ can

4 Silbert, S. Thrombo-Angitis Obliterans (Buerger). Treatment of Five Hundred and Twenty-Four Cases by Repeated Intravenous Injections of Hypertonic Salt Solution, Experience of Ten Years, Surg, Gynec & Obst **61** 214 (Aug) 1935

5 Maddock, W G, and Collier, F A. Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angitis Obliterans, Ann Surg **98** 70 (July) 1933

6 Barker, N W. Vasoconstrictor Effects of Tobacco Smoking, Proc Staff Meet, Mayo Clin **8** 284 (May 10) 1933

7 Wright, I S, and Moffat, D. The Effects of Tobacco on the Peripheral Vascular System, J A M A **103** 318 (Aug 4) 1934

8 Lampson, R S. A Quantitative Study of the Vasoconstriction Induced by Smoking, J A M A **104** 1963 (June 1) 1935

9 Mulinos, M G, and Shulman, I. Vasoconstriction in the Hand from a Deep Inspiration, Am J Physiol **125** 310 (Feb) 1939

be demonstrated by comparing the depth of respiration necessary to produce slight drops in the temperature of the finger tips as compared with the profound drops often caused by smoking with only mild or moderate inhalation

An attempt by Harkavy and his co-workers¹⁰ to place the effect of tobacco in thromboangitis obliterans on an allergic basis has been opened to serious question by the work of Trasoff, Blumstein and Marks¹¹ and that of Wescott and Wright¹²

Thus far, the only established mechanism involved is the physiologic one of constriction of the small arteries and arterioles. Even for the arteriosclerotic patient with already impaired circulation this is sufficient to interdict its use. Although spasm of the sclerotic vessels is not considered important, one must remember that the life of the tissues frequently depends on the collateral vessels, that these are usually not sclerotic and that they may be constricted by smoking. If, for example, the circulation in an extremity is already impaired to a fraction of its former potential, i. e., to the point at which life of the tissue is endangered, the deciding factor may be further constriction of the vessels, reduction of circulation and production of gangrene. This principle operates in all degrees, and in my opinion, indicates that patients with definitely impaired circulation from arteriosclerosis or any other cause should completely abstain from the use of tobacco.

The clinical evidence is even stronger in the cases of thromboangitis obliterans. In my experience and that of my associates, good results are to be expected from the general treatment outlined here provided the patient will completely stop smoking. The only 3 patients in our series of 100 cases of thromboangitis obliterans observed since 1931 on whom major amputations were performed continued to smoke surreptitiously even though warned many times of the dire consequences. Each of these 3 patients lost one leg. Patients who steal an occasional smoke usually have ulcers which are slow to heal, continue to ooze and look inflamed. If an ulcer has been healing nicely and it suddenly enlarges and begins to look inflamed, careful questioning will usually elicit a confession of a relapse to smoking. Numerous patients whose ulcers have been healed for from six months to several years have returned with a new ulcer and an admission that they had resumed smoking, after which, within

10 Harkavy, J., Hebard, S., and Silbert, S. Tobacco Sensitiveness in Thromboangitis Obliterans, *Proc Soc Exper Biol & Med* **30** 104 (Oct) 1932

11 Trasoff, A., Blumstein, G., and Marks, M. Immunologic Aspect of Tobacco in Thrombo-Angitis Obliterans and Coronary Heart Disease, *J Allergy* **7** 250 (March) 1936

12 Wescott, F. H., and Wright, I. S. Tobacco Allergy and Thromboangitis Obliterans, *J Allergy* **9** 555 (Sept) 1938

a few days or weeks, the pain and the ulcer returned. Results of therapy in this disease depend on the edict "Absolutely no smoking, now and forever!"

ALCOHOL

In contrast, the action of alcohol on the peripheral arteries is definitely vasodilating. In experiments performed in this laboratory,¹³ the rise in temperature of the tips of the extremities after ingestion of 60 to 90 cc of whisky has been as great as 9 to 12 degrees (F), depending in part on the condition of the vessels and the control temperature prior to the experiments. I feel, therefore, that the use of whisky or other spirituous liquors is indicated in the treatment of organic occlusive disease of the peripheral vascular system. There is general agreement in this at present among most of the leading clinics for vascular disease. The dose depends on the severity of the condition. With impending or actual gangrene the patient should receive enough to keep the peripheral vessels as much dilated as possible. In many cases he should be kept slightly inebriated during the critical period. This sometimes requires 30 to 60 cc (1 to 2 ounces) of whisky every four hours or more frequently. This may be tapered down as the emergency subsides to 30 to 60 cc once or twice a day, which is the dose usually recommended in cases of nonacute involvement. As Brown, Allen and Mahorner¹⁴ pointed out in addition to its vasodilatory properties whisky may control the pain of peripheral vascular disease in some cases more satisfactorily than morphine.

Unless there are definite contraindications, such as severe diabetes, gastric ulcer or alcoholism, I feel that patients with arteriosclerosis obliterans should have some alcoholic beverage each day for the remainder of their lives.

BATHS

The proper use of baths constitutes a definite contribution to the treatment of occlusive vascular disease. Baths may be grouped under several headings, as follows:

1 *Contrast Baths*—Perhaps the most generally used bath for this type of condition is the contrast bath. Two containers are placed side by side. They should be deep, reaching to the patient's knee. In one, water at 40.2 C (105 F) is placed. In the other, water of "tap water temperature," 15.5 to 20.1 C (60 to 70 F), is used. The legs are placed first in one and then in the other at intervals varying from one to three minutes. The last immersion should always be in the hot water. My

13 Wright, I. S., Poindexter, C., and Van Dellen, T. The Vaso-Dilating Effects of the Ingestion of Spirituous Liquors, unpublished data.

14 Brown, G. E., Allen, E. V., and Mahorner, H. R. *Thromboangitis Obliterans*, Philadelphia, W. B. Saunders Company, 1928.

associates and I have suggested seven alternations, beginning and ending with hot water. This treatment should be given once or twice a day, depending on the condition of the extremity. The theory is that the patent vessels are exercised by producing alternate vasoconstriction and vasodilation. There are, however, several objections to this type of bath, which have resulted in our abandoning its use. First, the best containers reach only to the knees. The blockage may be far above that level, so that, although the contrast baths may produce different metabolic demands, the ability to respond may not be realized at the level of the stimulus. Second, when already damaged vessels are forced into sudden vasospasm they may remain closed, complicating the picture considerably. Third, in our experience there is often severe pain during the cold phase, perhaps due to cramping or to ischemia. We have therefore adopted a modification of the long-used sitz bath for this purpose.

2 *Sitz Baths*—The patient sits in a tub containing at least 12 inches (30 cm) of water at a temperature of 37.8 to 40.2 C (100 to 105 F) for twenty to thirty minutes at least once a day. This overcomes all of the objections to the contrast bath. (Theoretically it does not exercise the small vessels as well.) The heat extends high enough to activate the collateral arteries from the trunk and also the femoral arteries. No cold water being involved, the risk of sudden permanent occlusion or of severe pain is minimized. If water of this temperature appears to cause discomfort, the temperature should be reduced to 34.4 to 36.7 C (94 to 98 F). This type of bath is not, of course, suitable for patients with open ulcers or gangrene, because of the risk of infection.

3 *Whirlpool Baths*—Whirlpool baths, if available, may further stimulate the circulation, the motion of the water being especially helpful in the presence of chronic low grade ulceration. The temperature of the water should be about the same as for the sitz bath. Whirlpool baths usually have the objection of not extending high enough on the limb.

4 *Soaks*—Wet dressings have largely been abandoned in this clinic because of their tendency to cool even under the most favorable conditions. This produces vasoconstriction and thus does more harm than good by defeating the chief aim, that of improving the circulation to the dying cells. In their place, for ulcerated or gangrenous extremities we use soaks of boric acid solution or physiologic solution of sodium chloride at 35.7 to 37.8 C (96 to 100 F). These may be applied two or three times daily for fifteen to thirty minutes. After each soak the foot is removed, dried carefully and placed under a warm lamp cradle at 33.2 to 35.4 C (92 to 96 F) to prevent chilling. The object should be to allow proper drainage by softening and cleaning away crusts which tend to lock in infection, but once infection is under control attempts

should be steadily made to produce a dry lesion rather than a wet, macerated one. Healing is made more rapid and the danger of infection is reduced when the lesion is dry.

HEAT

1 *Local Heat*—The problem of heat is one of great importance in the handling of arteriosclerosis and thromboangitis obliterans. It is probable that in the past heat has done more harm than good, because of improper use. Properly handled, it tends to reproduce normal temperature. The normal surface temperature rarely exceeds 39.9 to 35.6 C (93 to 96 F). In order to achieve this and hence stimulate normal metabolic processes the temperature of the environment should approximate that level. My associates and I therefore use thermostatically controlled heat cradles¹⁵ which keep the temperature between 34.4 and 35.7 C (94 and 96 F). By careful watching and the use of a thermometer an equal distance between the lamp and the extremity it is possible to use ordinary light bulbs, but the factor of error is great, and the disease in many cases has been greatly aggravated by overheating. As Starr¹⁶ has pointed out, increasing the metabolic demands beyond the capacity of the supplying arteries leads to increasing gangrene. Controlled heat within these limits is, in our opinion, the only safe form of heat for use in this condition. The local use of heat lamps, diathermy or short wave machines is to be condemned. I have seen in consultation many patients with severe ulceration, massive necrosis or gangrene which appeared to have been precipitated by such measures, 7 of these patients lost their legs, and 2 died—not primarily as a result of vascular disease but rather of the results of the misapplied treatment. I have emphasized this previously.¹⁷

2 *Reflex Heat*—Using a modification of the principle employed by Gibbon and Landis,¹⁸ my associates and I have used reflex heat as a therapeutic measure as well as to determine the potential vasodilatation of the vascular tree. After trying several approaches, we have found the simplest effective technic to be merely the application of an electric heating pad over the abdomen for thirty to sixty minutes once or twice a day. Optimum dilatation of the vessels of the extremities (considering the disease present) is thus obtained. Greater heat (the maximum com-

15 Those used by us were made by the Valverde Laboratories, of New York.

16 Starr, I, Jr. A Thermoregulated Foot Cradle for the Treatment of Peripheral Vascular Disease, *Proc Soc Exper Biol & Med* **29** 166 (Nov) 1931.

17 Wright, I S. Physical Therapy in Peripheral Vascular Disease, *Arch Phys Therapy* **19** 161 (March) 1938.

18 Gibbon, J H, Jr, and Landis, E M. Vasodilatation in Lower Extremities in Response to Immersing Forearms in Warm Water, *J Clin Investigation* **11** 1019 (Sept) 1932.

patible with the safety and comfort of the patient) should be used with this device, as the dilation occurs from the proximal toward the distal ends of the extremities. If diathermy, short wave therapy or infra-red rays are to be used for these conditions, their application should be to the trunk to produce reflex vasodilatation.

Wilkins, Doupe and Newman¹⁹ have shown by means of plethysmographic studies of the fingers that the increase in blood flow resulting from local heat is not as great as that produced by warming the body.

TYPHOID VACCINE

In our experience typhoid vaccine given intravenously in the manner to be outlined is of great value in the treatment of thromboangitis obliterans. We have been cautious in its use for arteriosclerosis and have recommended it only when all other methods have proved inadequate to control progression toward gangrene. In a few cases it has been possible to reverse the process, producing marked improvement, but, although we have had no accidents, we are inclined to fear coronary or cerebral thrombosis as a complication.

The action of typhoid vaccine is nonspecific, probably depending purely on vasodilation of the available functioning main and collateral vessels supplying the limb. The use of nonspecific foreign protein therapy was first suggested by Goodman and Gottesman²⁰ in 1923 and was advocated by Brown,²¹ Allen and others. It is now one of the most widely accepted forms of therapy for thromboangitis obliterans. Until 1931 Brown and Allen used triple typhoid vaccine (typhoid and paratyphoid A and B strains, Lederle). Barker²² in 1931 described "typhoid H" antigen (Lilly), a fraction of the typhoid bacterium prepared by emulsifying the organisms in sodium chloride solution and subsequently killing them with 0.5 per cent phenol. The results seemed better than with the triple typhoid vaccine, and the untoward effects were less.

My associates and I have used with good results and minimal untoward effects a typhoid vaccine prepared especially for this purpose according to our direction.²³ It is prepared from typhoid bacilli exclusively and is diluted to the strength of 100,000,000 organisms per cubic

19 Wilkins, R. W., Doupe, J., and Newman, H. W. The Rate of Blood Flow in Normal Fingers, *Clin. Sc.* 3: 403 (Dec.) 1938.

20 Goodman, C., and Gottesman, J. Pain and Its Treatment in Thromboangitis Obliterans, *New York M. J.* 117: 774 (June 20) 1923.

21 Brown, G. E. The Treatment of Peripheral Vascular Disturbances of the Extremities, *J. A. M. A.* 87: 379 (Aug. 7) 1926.

22 Barker, N. W. Results of Treatment of Thrombo-Angitis Obliterans by Foreign Protein, *I. A. M. A.* 47: 841 (Sept. 19) 1931.

23 The vaccine was prepared by the Kirk Biological Laboratories, of Bloomfield, N. I.

centimeter. This dilution permits more accurate measurements of the dose than do the more concentrated solutions in routine use. Severe reactions have been caused in the past by attempts to measure accurate doses of typhoid vaccine from too concentrated a suspension, the fact being forgotten that suspensions tend to settle and vary in concentration unless they are shaken thoroughly before use. The risk is minimized by using low concentrations and shaking well. The procedure used is as follows. The first dose is 5,000,000 organisms. Injections are given every three days, provided that the effect of the preceding dose has completely worn off. The object is to obtain a rise in oral or rectal temperature of 2 or 3 degrees F (1 or 2 degrees C) without a chill. Although usually a slight drop in surface temperature precedes the rise, this is inconsequential if no chill occurs. The rise in surface temperature of the tips of the extremities with this fever is from 3 to 4 degrees C (4 to 6 degrees F), but of course it is affected by the degree of occlusion of the total arterial supply to the limb, including the collateral vessels.

When a dose of 5,000,000 organisms fails to produce a satisfactory fever, the dose is increased to 10,000,000 and kept at that level as long as the reactions are satisfactory. Increases of 3,000,000 to 5,000,000 organisms are made whenever the effects of the preceding dose are inadequate, otherwise the dose is repeated at the same level. If the temperature goes above 39.5 C (103 F) and a chill occurs, the next dose is decreased by 3,000,000 to 5,000,000. Doses have been increased up to 200,000,000 or more, but with most patients a top level of 70,000,000 to 130,000,000 seems to be reached, and administration can be continued indefinitely at that level. Proceeding carefully in this manner, with over 12,000 injections we have had no serious untoward effects attributable to the treatment. During acute infection or other serious illness this treatment has been suspended.

The results following the use of this technic have been gratifying. Relief of the pain associated with small ulcers has occurred after the first, second or third injection, and rapid healing has taken place. The major gangrenous processes naturally respond more slowly, but the results appear to us to be more rapid than are those of intravenous administration of saline or citrate solutions. These methods will be discussed

INTRAVENOUS ADMINISTRATION OF SALINE SOLUTION AND OTHER SOLUTIONS

Since the observation of Mayesima²⁴ that the viscosity of the blood is increased in thromboangitis obliterans, various solutions have been used on the theory that reduction of the viscosity would have a favorable

²⁴ Mayesima, J. Klinische und experimentelle Untersuchungen über die Viskosität des Blutes, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **24** 413, 1911-1912.

effect on the course of the disease Koga²⁵ in 1913 was the first to introduce intravenous therapy for the treatment of thromboangitis obliterans, using physiologic solution of sodium chloride in some cases and Ringer's solution in others Willy Meyer²⁶ in 1916 was the first American to adopt this method, using the same solutions Ginsburg²⁷ in 1917 and Steel²⁸ in 1921 used sodium citrate Various other solutions have been tried, but the most widely used at present is hypertonic (3 to 5 per cent) solution of sodium chloride as introduced by Silbert²⁹ in 1926 The dose is usually 300 to 400 cc of 3 per cent solution given intravenously three to seven times a week The results have repeatedly been reported on favorably by Silbert³⁰ and by Samuels³¹ The action of the substance has not been clearly demonstrated, although various explanations have been advanced, namely, reduced viscosity, increased pulse volume and vasodilation A uniform increase in the surface temperature is not observed

After study, intravenous injections of large volumes of saline or citrate solution has been abandoned by numerous workers in favor of the other forms of therapy outlined here In my experience and that of my associates, the use of typhoid vaccine results in a quicker response, prompt relief of pain and more satisfactory healing

Hypertonic saline solution (especially the 5 per cent solution) may produce venous thrombosis, chills and hepatitis Although we do not consider it the treatment of first choice, there may be patients with thromboangitis obliterans for whom it should be tried when typhoid vaccine is contraindicated or when response to it does not appear satisfactory The use of this substance has thus far no sound theoretic basis in the treatment of arteriosclerosis and is not recommended at this time

25 Koga, G Zur Therapie der Spontangangran an den Extremitäten, *Deutsche Ztschr f Chir* **121** 371, 1913

26 Meyer, W The Conservative Treatment of Gangrene of the Extremities Due to Thrombo-Angitis Obliterans, *Ann Surg* **63** 28 (March) 1916

27 Ginsburg, N A Consideration of the Treatment of Peripheral Gangrene Due to Thrombo-Angitis Obliterans, *Am J M Sc* **154** 328 (Sept) 1917

28 Steel, W A Sodium Citrate Treatment of Thrombo-Angitis Obliterans, *J A M A* **76** 429 (Feb 12) 1921

29 Silbert, S The Treatment of Thrombo-Angitis Obliterans by Intravenous Injection of Hypertonic Salt Solution, *J A M A* **86** 1759 (June 5) 1926

30 Silbert, S Thrombo-Angitis Obliterans Results of Treatment with Repeated Injections of Hypertonic Salt Solution, *J A M A* **94** 1730 (May 31) 1930, footnote 4

31 Samuels, S Gangrene Due to Thrombo-Angitis Obliterans, *J A M A* **102** 436 (Feb 10) 1934

SODIUM CITRATE, RINGER'S SOLUTION AND INSULIN

The use of sodium citrate, Ringer's solution and insulin for the treatment of thromboangitis obliterans and arteriosclerosis is being given up in most clinics being confined to a few scattered institutions. I therefore feel that further discussion of these substances is not indicated.

VASODILATING DRUGS

Numerous drugs have been used in the treatment of thromboangitis obliterans and arteriosclerosis obliterans on the basis of their vasodilating powers. The more common of these may roughly be divided into

- 1 The nitrites and allied compounds
- 2 The theobromines, theocalcine (a mixture of calcium theobromine and calcium salicylate) and allied compounds
- 3 The choline compounds
- 4 Papaverine

After years of study, both clinical and experimental with all of these substances it seems fair to state that the value of their use singly or collectively in the treatment of these conditions is relatively limited.

Briefly, the action of the nitrites is too fleeting, and the dilatation as it affects the vessels of the extremities is observed with difficulty.

The action of theobromine and its allied compounds in the usual doses is unreliable and doubtful.³²

The action of certain of the choline compounds, although of established value in the treatment of certain diseases of the peripheral circulation, such as varicose ulcers, appears to be of no value in the treatment of arteriosclerosis and to be useful only rarely in the treatment of thromboangitis obliterans.³³

Papaverine has been advocated for the relief of sudden occlusion and for its general vasodilating qualities.³⁴ In a recent study Littauer and

32 McGovern, T, McDevitt, E, and Wright, I S. Theobromine Sodium Salicylate as a Vaso-Dilator, *J Clin Investigation* **15** 11 (Jan) 1936

33 Saylor, L, Kovacs, J, and Wright, I S. The Pharmacological and Therapeutic Effects of Certain Choline Compounds, *Am Heart J* **11** 53 (Jan) 1936. Saylor, L, Kovacs, J, Duryee, A W, and Wright, I S. Treatment of Chronic Varicose Ulcers by Means of Acetyl-Beta-Methylcholine Chloride Iontophoresis, *J A M A* **107** 114-117 (July 11) 1936

34 Denk, W. Zur Behandlung der arteriellen Embolie, *Munchen med Wchnschr* **81** 437 (March) 1934. Allen, E V, and MacLean, A R. Treatment of Sudden Arterial Occlusion with Papaverine Hydrochloride, *Proc Staff Meet, Mayo Clin* **10** 216 (April 3) 1935. deTakats, G. The Use of Papaverine in Acute Arterial Occlusions, *J A M A* **106** 1003 (March 21) 1936

I³⁵ have found its vasodilating effects to be highly unreliable and not nearly so marked as the effect of simple reflex heat. The relaxing effect of papaverine and other opiates and the value of this relaxation are undoubted. Such preparations should be used wisely and with the possibility of ultimate habituation in mind, although this danger has proved to be a serious factor only once in our experience. Morphine should be used only as a last resort, because of the familiar objections of nausea, distention and habituation.

The long-standing use of potassium iodide in the treatment of arteriosclerosis merits its mention here, although clinically I have been unconvinced of its value. Animal experiments have seemed to demonstrate that it will prevent the actual laying down of cholesterol. This has not, however, been proved to be a process comparable to arteriosclerosis in man.

TISSUE EXTRACTS

The therapeutic use of various tissue extracts was stimulated by the studies of Frey and Kraut³⁶ and Gley and Kisthinos³⁷ and in the United States by the work of Wolffe³⁸ Elliot and Nuzum,³⁹ Barker, Brown and Roth,⁴⁰ Duryee⁴¹ and others. Although at first emphasis was directed toward the effect of these extracts on the anginal syndrome, this proved difficult to evaluate, and more recently increasing interest has developed in the more easily measured response of the syndrome of intermittent claudication to their use. During the past six years my associates

35 Littauer, D, and Wright, I S. The Questionable Value of Papaverine Hydrochloride in the Treatment of Peripheral Vascular Disease, *Am Heart J* **17** 325 (March) 1939.

36 Frey, E K, and Kraut, H. Ueber einen von der Niere ausgeschiedenen, die Herztaetigkeit anregenden Stoff, *Ztschr f physiol Chem* **157** 32, 1926, Ein neues Kreislaufhormon und seine Wirkung, *Arch f physiol Chem* **175** 97, 1928. Frey, E K. Kreislaufhormon und innere Sekretion, *Munchen med Wchnschr* **76** 1951 (Nov 22) 1929.

37 Gley, P, and Kisthinos, N. Recherches sur la substance hypotensive du pancreas, *Presse med* **37** 1279 (Oct 2) 1929.

38 Wolffe, J B. The Therapy of Tissue Extract ("Desympatome"), *Tr Am Therap Soc* **31** 31, 1931, Further Studies on Tissue Extract No 568 (Desympatome), *ibid* **34** 163, 1934.

39 Elliot, A H, and Nuzum, F R. The Pharmacologic Properties of an Insulin-Free Extract of Pancreas and the Circulator Hormone of Frey, *J Pharmacol & Exper Therap* **43** 463 (Nov) 1931, Pancreatic Extract in the Treatment of Angina Pectoris and Intermittent Claudication, *Arch Int Med* **49** 1007 (June) 1932.

40 Barker, N W, Brown, G E, and Roth, G M. Effect of Tissue Extracts on Muscle Pains of Ischemic Origin (Intermittent Claudication), *Am J M Sc* **189** 36 (Jan) 1935.

41 Duryee, A W. Tissue Extract in the Treatment of Peripheral Vascular Disease, *Tr Am Therap Soc* **35** 124, 1935.

and I have been using various extracts prepared from the pancreas, heart, skeletal muscle and liver. Certain of these proved on physiologic and clinical studies to be active, but they were for the most part rather crude, poorly standardized, high in protein content and painful to inject. Various fractions have been tried, and for the past year and a half we have been using a deproteinated pancreatic extract⁴². It is a colorless saline solution of a chemically purified, protein-free, nitrogenous fraction derived from an acid alcohol extract of beef pancreas. Physiologic tests show that it is apparently free from insulin, histamine and acetylcholine. It contains approximately 2.5 per cent of solids, including 0.25 per cent of nonprotein nitrogen, 0.9 per cent of sodium chloride and 0.25 per cent of phenol as a preservative. It is adjusted to a p_H of 6.5 to 6.8.

It is assayed by comparing its effect with that of a standard preparation on the arterial blood pressure of anesthetized dogs. This standard preparation is of such potency that in a large series of dogs 1 cc. produces an average lowering of arterial blood pressure equal to that produced by 0.01 mg. of epinephrine in the same dogs. The standard preparation is preserved by the lyophil process and stored in the dried state at 5°C. Each new lot of deproteinated pancreatic extract is standardized by comparing its depressor effect with that of a solution of the standard preparation on the normal and on the atropinized dog. The physiologic action of each lot is also studied by means of the heart-blocking effect in mice. Two cubic centimeters of "depropanex" is injected into white female mice, and an electrocardiograph is used to ascertain whether heart block occurs. The material is injected intraperitoneally and should not cause death from heart block in any of at least 3 mice within fifteen minutes.

A preliminary report of its effects on intermittent claudication in man, measured by an ergometer and by walking ability as measured in blocks (less accurate), has recently appeared (Fisher, Duryee and Wright⁴³). Controlled ergometric tests were continued to the point of production of such pronounced pain that the patient was forced to stop. After the length of time necessary for this had been rechecked, an injection of 3 cc. of deproteinated pancreatic extract was given. Thirty minutes later another ergometric test was made. The results of this series of experiments were as follows: Of 8 patients with untreated uncomplicated arteriosclerosis obliterans, 6 showed lengthening of the claudication time, of 5 patients with untreated but complicated arteriosclerosis, 4 showed improvement, and of 14 patients previously treated (for complicated and uncomplicated conditions) 13 showed improvement.

42 This substance, "depropanex," was supplied by Sharp and Dohme.

43 Fisher, M. M., Duryee, A. W., and Wright, I. S. Deproteinated Pancreatic Extract (Depropanex) Effect in the Treatment of Intermittent Claudication Due to Arteriosclerosis Obliterans, *Am Heart J* 18: 425 (Oct.) 1939.

after these initial studies. The improvement after the first injection was fleeting, the effect having worn off within twenty-four hours. Injections of saline solution were given as controls to each patient (without his knowledge), with absolutely negative results. The lengthening of the claudication time may be found in detail in the original paper. The average time prior to the injections ranged from one minute and twenty-six seconds to one minute and forty-three seconds in the various groups. In the half-hour tests the time averaged more than three minutes and one second. After ten or more such injections given intraglutely three times each week the effects were more pronounced and more prolonged as measured on the ergometer. This coincided with the improvement in walking ability reported by the patients.

In a purely clinical study of 100 patients who were followed for four to six months while they received triweekly injections, 74 reported definite clinical improvement, 26 failed to show sufficient improvement to warrant continued use of the extract. A warning should, however, be issued against accepting such clinical studies without proper weighing of the facts. Certain of the patients had been previously treated with a regimen for vascular disease, and this furnished a valuable control period. In other instances, however, as the patient had been recently placed on such a regimen, the improvement may have been partly due to the regimen alone or may have been merely the occasional remission which may occur spontaneously in this condition. No untoward effects have been noted in more than a thousand injections. We have given 48 to 100 cc of the substance intravenously to rabbits before producing death, whereas 4 to 15 cc of the former tissue extracts produced collapse and even death. We have given 3 cc intravenously to 20 patients, with no ill effects. Although we do not advocate this method of administration at present, it serves as an indication of the relative nontoxicity of the extract.

The mechanism of the action of pancreatic tissue extracts has never been satisfactorily explained, although a hormonal or replacement action similar to that of insulin is popularly assumed at present. Assay methods with animals (in which an antagonistic action to epinephrine has been demonstrated) indicate a factor of vasodilatation. This effect has not, however, been noted in man. My associates and I are engaged in studies which may clarify this problem. Some light may be shed on it by certain preliminary studies conducted by us and dealing with the effect of deproteinated and other pancreatic extracts on the experimental production of atherosclerosis in rabbits.⁴⁴ The results will be reported in detail elsewhere, but (in summary) four groups of rabbits have been studied, with the results given in tables 1 and 2.

⁴⁴ Fisher, M. M., Wright, I. S., Member, S., and Durvee, A. W. Unpublished data.

The animals were killed in from four to sixteen weeks. The data in the tables were obtained at autopsy.

The deposition of cholesterol to produce atherosclerosis of the aorta is seen to be markedly retarded by the use of pancreatic tissue extracts⁴⁵. The extracts do not prevent the deposit of fat in the liver. It should

TABLE 1—*Gross Atherosclerosis of the Aorta and Deposits of Fat in the Liver*

Group	Grade (1 to 4+)										Average
	Aorta										
1a (10 control rabbits, regular purina chow)†	Aorta	0	0	0	0	0	0	0	0	—	0
	Liver	0	0	0	0	0	0	0	0	—	0
2a (6 rabbits regular purina chow + 3 cc pancreatic extract given intramuscularly 3 times per week)	Aorta	0*	0†	0†	0†	0*	0*				0
	Liver	0	0	0	0	0	0				0
1b (7 rabbits, regular purina chow + 1 Gm cholesterol 3 times per week)	Aorta	4+	3+	4+	4+	4+	4+	4+			3.9+
	Liver	4+	±	1+	4+	4+	4+	4+			3.5+
2b (6 rabbits regular purina chow + 1 Gm cholesterol 3 times per week and 3 cc pancreatic extract given intramuscularly 3 times per week)	Aorta	3*	0†	0†	0†	0*	0*				0.5
	Liver	4+	4+	3+	4+	2+	3+				3.3+

* Grant's pancreatic hormone lot 66. This is a pancreatic extract similar in many respects to the former pancreatic tissue extract no. 568 of Sharpe and Dohme. It is free from insulin but not from protein. It has a favorable effect on the syndrome of intermittent claudication. It is prepared by the Grant Chemical Company of Philadelphia and New York.

† Deproteinized pancreatic extract.

‡ This preparation is made by the Ralston Cereal Company, of St. Louis. It is a mixture of grains and alfalfa hay supplemented by vitamins and minerals. It is said to contain iodized salt, but the amount of iodine present seems to be very small, since it in no way interfered with the disposition of cholesterol in the arteries of any of the control animals fed cholesterol.

TABLE 2—*Cholesterol Content of the Aorta at Autopsy*

Group	Cholesterol, Gm per 100 Cc									Average
1a	0.444	0.420	0.400	0.470	0.590	0.360	0.360	0.750	0.460	0.4726
2a	0.748*	0.456†	0.288†	0.710†	0.205*	0.191*				0.43±0
1b	7.610	1.217	2.052	2.233	10.791	7.568	15.441			6.7017
2b	3.156*	1.130†	0.969†	0.742†	0.616*	0.438*				1.2059

* Grant's pancreatic hormone, lot 66.

† Deproteinized pancreatic extract.

be recognized, however, that this type of atherosclerosis, although similar, has not been proved to be exactly identical to human senile atherosclerosis and also that certain other substances, including lipocac,⁴⁶ have been reported to have similar properties. Studies of the blood

⁴⁵ This has been previously observed by Samuelson, who used other pancreatic extracts.

⁴⁶ Huber, M. J., Broun, G. O., and Casey, A. E. Prevention of Cholesterol Arteriosclerosis in Rabbits by Use of Pancreatic Extract (Lipocac), *Proc Soc Exper Biol & Med* **37** 441 (Dec.) 1937.

cholesterol were also made. The results were not striking, although some degree of temporary lowering of the level of cholesterol was noted, and the general average for the series was lower for the rabbits fed cholesterol and receiving tissue extract than for those receiving cholesterol but no tissue extract. More extensive animal and clinical studies will be necessary for final evaluation of this substance. Other fractions may prove more potent. At present the one in use appears to be nontoxic, its administration is practically painless, and it is of some value in the treatment of certain patients with the syndrome of intermittent claudication. Further studies regarding the mechanism of its action and the clinical problems of dosage, duration of action and effect are being carried on at our clinic and elsewhere.

MECHANICAL THERAPY

The "Vas-Oscillating Bed" (Sanders)—A form of mechanical treatment which has recently been used in a number of clinics is the motor bed described by Sanders⁴⁷. By means of this bed the head and feet of the patient are alternately elevated and lowered, a complete cycle taking from one to three minutes. The movement is smooth, the patient soon becomes accustomed to it, and we have had patients on these beds for as long as two years. Most of them have continued its use during the sleeping hours long after their open lesions have healed. The degree of tilting and the speed of the cycle can be regulated within reasonable limits. The object is to exercise the arteries which are still able to function by producing rubor and pallor (engorgement and ischemia), as with the Buerger exercises, but continuously and without fatigue to the patient. This process is gentle, involves no constricting bands and appears theoretically sound, especially for the treatment of arteriosclerosis with or without gangrene. My associates and I use a thermostatically controlled cradle at 96 F (35.7 C) for adjunct treatment. While the total experience with this equipment has been rather limited, we have now had the opportunity to study about 50 cases. Clinical impressions are often deceptive guides, and experimental studies are not available, but so far the workers in our clinic and in other clinics⁴⁸ have been favorably impressed. Healing of ulcers has taken place in certain patients after complete failure of the pressure-suction boot and the reactive hyperemia machine. Many patients can use this equipment who are made very uncomfortable by the action of the boot or cuff. Thus far the condition indicating its use appears to be advanced

47 Sanders, C. E. Cardiovascular and Peripheral Vascular Diseases. Treatment by a Motorized Oscillating Bed, J. A. M. A. **106** 916 (March 14) 1936.

48 Baker, N., and Roth, G. Treatment of Occlusive Arterial Disease of Legs by Means of Saunders Vasocillator (Saunders Bed), Am. Heart J. **18** 312 (Sept.) 1939.

arteriosclerosis of the vessels of the legs with impending or actual early gangrene. The results in certain cases of such involvement have been encouraging in that the symptomatic progress of the condition has been checked and reversed, with improvement and healing. We should like to suggest a thorough study of the possibilities of this treatment for cerebral arteriosclerosis, for which to date there has been no treatment of sufficient value to be taken seriously.

Progress in this type of case is slow, and we find it usually necessary to keep the patient on the bed for at least one month. In our experience, treatments of a few hours' duration are not satisfactory. We have set a minimum in our clinic of eight hours a day. Use of the bed for patients with thromboangitis obliterans seems rarely necessary, since the proper use of typhoid vaccine is satisfactory in most cases.

PRESSURE SUCTION BOOT

Although variations in environmental pressure have been used in the treatment of impaired circulation since before 1800, it remained for Landis and Gibbon⁴⁹ and Herrmann and Reid⁵⁰ to perfect suitable mechanical apparatus and to popularize this principle for widespread use in the treatment of peripheral vascular disease.

The principle on which the modern apparatus is established depends on the hypothesis that blood flow in an extremity can be increased appreciably by exposing the extremity to fluctuations in pressure from positive to negative and back to positive, continuing such alternations for the duration of the treatment, which may be from one to twenty-four hours or more. The extremity is contained in a so-called boot made of glass or metal in which the pressure changes are produced by means of connections to a correctly constructed air pump system. The opening through which the leg is inserted is made air tight by means of any of a number of types of rubber cuff. There have been certain disagreements as to the type and timing of the cycle to be used and the amounts of pressure and suction desirable. At present the most commonly used cycle approximates those suggested by Herrmann and is

49 Landis, E. M., and Gibbon, J. H., Jr. The Effects of Alternating Suction and Pressure on Circulation in the Lower Extremities, *Proc Soc Exper Biol & Med* **30** 593 (Feb) 1933, The Effects of Alternate Suction and Pressure on Blood Flow to the Lower Extremities, *J Clin Investigation* **12** 925 (Sept) 1933.

50 Herrmann, L. G. Syphilitic Peripheral Vascular Diseases. Treatment by Means of an Intermittent Negative Pressure Environment, *Am J Syph* **17** 305 (July) 1933. Herrmann, L. G., and Reid, M. R. The Pavaez (Passive Vascular Exercise) Treatment of Obliterative Arterial Diseases of the Extremities, *J Med* **14** 524 (Dec) 1933. Herrmann, L. G. *Passive Vascular Exercises*, Philadelphia, J. B. Lippincott Company, 1936.

as follows With atmospheric pressure as the base line, one complete cycle takes fifteen seconds The first three second period is one of positive pressure, reaching gradually 20 mm of mercury There is then a gradual downward curve, crossing the base line in the third second and proceeding to a negative pressure of —80 mm of mercury at the eleventh second A more rapid return to the base line completes the cycle in fifteen seconds This is, of course, repeated continuously for the duration of each treatment

Certain objections had to be met to make this treatment satisfactory theoretically and practically In order to operate the boot the cuff around the upper part of the extremity must be air tight This produces a certain degree of constriction about the limb and hence interferes with the blood flow, especially in the superficial vessels Many types of cuff have been devised, and some have overcome this objection at least partially

In general, when the circulation to an extremity is increased there is an increase in the surface temperature of that extremity It has been noted in our clinic and elsewhere that the temperature of the limb is often colder after this type of treatment than before This may be due to the aforementioned constriction or to the continuous flow of air in and out of the boot As a result of that observation, local or reflex heat has been used, with improvement in this regard The degree of dilatation depends on the potential capacity of the vessels, damaged and undamaged As with all new or rediscovered methods of treatment, the first claims for this method represented a somewhat optimistic picture of its usefulness It was stated that it was of great value for arteriosclerosis (senescent and diabetic), thromboangitis obliterans, Raynaud's disease, acute embolism, frostbite and other forms of circulatory impairment Actual experience with this apparatus has, in my opinion, greatly narrowed the indications for its use At present I feel that it may be useful in selected cases of uncomplicated senescent or diabetic arteriosclerotic gangrene, acute embolism or thrombosis and frostbite Even for certain of these conditions I must confess that I am not absolutely convinced as to its value On the other hand, certain contraindications for its use have been definitely established

Pressure suction should never be used in the presence of an acute or subacute infectious process or of any form of acute or subacute thrombophlebitis (which includes most forms of thromboangitis obliterans) or in any case in which evidence of autolysis of the tissues is noted, such as a case of acute embolism or thrombosis (e g, arteriosclerotic sudden occlusion) in which after several days the skin becomes mottled and blistered In these conditions the results of its use may be serious It appears futile to use it when the level of application of

the cuff is peripheral to the level of arterial blockage, yet this is being done constantly Allen and Brown,⁵¹ Conway⁵² and Wilson and Roome⁵³ reported unsatisfactory results in the treatment of thromboangitis obliterans, and even Reid and Herrmann⁵⁴ have recently stated that they were no longer so enthusiastic as to the ultimate results. My associates and I do not use it in the treatment of thromboangitis obliterans, having observed more satisfactory results with typhoid vaccine.

Kountz⁵⁵ reported pressure suction to be of little value in experimental and clinical studies and devised an apparatus with a series of cuffs to be applied serially the length of an extremity, these to be operated in sequence and tending to "milk" the blood along the limb. Increasing the temperature up to 40 C (104 F) increased the flow about 8 per cent in normal but less in diseased extremities. Iontophoresis produced a similar response. Kountz and Smith⁵⁶ reported encouraging results with this equipment in 23 cases of arteriosclerosis and thromboangitis obliterans. Their results are difficult to interpret, however, because in addition to this mechanized treatment (a) hypertonic saline solution was given intravenously twice a week, (b) alcohol was given daily by mouth and (c) patients with thromboangitis obliterans received typhoid vaccine intravenously.

Further, more carefully controlled studies must be done to evaluate this type of equipment. I have had no personal experience with it.

REACTIVE HYPEREMIA AND INTERMITTENT VENOUS OCCLUSION

The phenomenon of "reactive hyperemia" has long been recognized. Among the early descriptions are those of Cohnheim⁵⁷ and Lister⁵⁸

51 Allen, E. V., and Brown, G. E. Intermittent Pressure and Suction, *J. A. M. A.* **105** 2029 (Dec 21) 1935.

52 Conway, J. H. Obliterative Vascular Disease. Report of Fifty-One Cases Treated with Passive Vascular Exercise, *J. A. M. A.* **106** 1153 (April 4) 1936.

53 Wilson, H., and Roome, N. W. Passive Vascular Exercise. Observation on Its Value in the Treatment of Peripheral Vascular Diseases, *J. A. M. A.* **106** 1885 (May 30) 1936.

54 Reid, M. R., and Herrmann, L. G. Non-Operative Treatment of Peripheral Vascular Diseases, *Ann. Surg.* **102** 321 (Sept.) 1935.

55 Kountz, W. B. Re-Establishment of the Circulation in Extremities, *Arch. Phys. Therapy* **20** 157 (March) 1939.

56 Kountz, W. B., and Smith, J. R. Observations on Passive Vascular Exercise and Other Forms of Treatment of Peripheral Vascular Disease, *Am. Heart J.* **16** 55 (July) 1939.

57 Cohnheim, J. Untersuchungen über die embolischen Prozesse, Berlin, A. Hirschwald, 1872.

58 Lister. *Bull. Acad. de med., Paris* **8** 640, 1878, cited by Lewis and Grant⁶⁰

The superficial manifestation is a bright flush of the skin which occurs after release of a circulatory obstruction. Bier⁵⁹ studied this phenomenon for many years and developed therapeutic procedures based on the principle that obstruction and then release of the circulation would produce a marked circulatory increase and that this would be beneficial for certain pathologic states. This reflex was at first thought to result from vasomotor paralysis produced by pressure of the constricting band on the nerves, but Bier demonstrated that it can occur when every connection between the limb and the body has been severed except the artery itself. (This apparently does not, however, include severance of the sympathetic nerves of the arterial wall.) Lewis and Grant⁶⁰ showed that hyperemia of the skin occurs on restoration of the circulation even though the cutaneous nerves have degenerated. Anesthetic skin cannot be differentiated by its reaction from normal skin. The reaction appears to be independent not only of the central nervous system but of local nervous reflexes.

Bier⁵⁹ and Zak⁶¹ expressed the opinion that when the circulation is occluded the venous blood stagnating in the vessels causes them to contract and that "reactive hyperemia," which follows release of the circulation, is a direct response of the vessels to the incoming blood.

Katzenstein⁶² and Krogh⁶³ disagreed with this hypothesis, the latter especially taking exception to the theory that venous blood causes vessels to constrict while arterial blood causes them to dilate. Bier's conception depends on the supposition that the tone of the vessels is increased during occlusion and decreased when arterial blood enters them. Lewis and Grant have, however, presented evidence that this is not so and that dilatation of the vessels responsible for the cutaneous hyperemia occurs during the occlusion and not at the release.

The exact mechanism by which this takes place has been difficult to determine, involving, as it probably does, complex intracellular and extracellular chemical problems. As Roy and Brown⁶⁴ pointed out, it

59 Bier, A. *Hyperamie als Heilmittel*, ed 2, Leipzig, F. C. W. Vogel, 1905, *Contributions to the Physiology and Pathology of Circulation*, translated by J. B. Linn, New York, privately printed, 1905.

60 Lewis, T., and Grant, R. *Observation upon Reactive Hyperemia in Man*, *Heart* **12** 73 (June) 1925.

61 Zak, E. *Ueber den Gefasskrampf bei intermittierenden Henken und uber gewisse papillomotorische Erscheinungen*, *Wien Arch f inn Med* **2** 405 (June) 1921.

62 Katzenstein, M. *Ueber Entstehung und Wesen des arteriellen Collateral-kreislaufs*, *Deutsche Ztschr f Chir* **77** 189, 1905.

63 Krogh, A. *The Anatomy and Physiology of Capillaries*, New Haven, Yale University Press, 1922.

64 Roy, C. S., and Brown, J. G. *The Blood-Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins*, *J. Physiol* **2** 323, 1879, cited by Lewis and Grant⁶⁰.

represents an attempt on the part of tissues deprived of a proper blood supply to become repossessed of it

It should be emphasized that hyperemia represents a phenomenon which is constantly occurring. The part which bears the weight of the body necessarily becomes ischemic. When one moves about, shifting the weight, there is a flood of blood into the ischemic tissues to compensate for the accumulated debt to local metabolism. When the weight is too constantly on certain areas or when the vascular tree does not permit this compensation, necrosis occurs. Lewis and Grant⁶⁰ published instructive studies of this phenomenon as it occurs after both arterial and venous obstruction and release. Recent interest in the subject warrants a brief review of certain of their pertinent observations. In relation to *arterial* reactive hyperemia these authors reached the following conclusions:

- 1 Increase in the environmental temperature within certain limits produces a definite increase in the response, e. g., with temperatures of 15 to 20 C the increase in flow on release of the constriction was 2 cc. in 600 cc. of tissue, whereas at a temperature of 40 C an identical plethysmographic experiment produced an increase of 15 to 20 cc. of blood flow per minute to 600 cc. of tissue. It is thus very important that in all such studies the temperature should be carefully controlled.

- 2 Within certain limits, the longer the duration of occlusion the greater is the duration of the subsequent hyperemia. The flush usually lasts approximately one-half to three-quarters as long as the preceding occlusion. Occlusion lasting more than twenty minutes is very uncomfortable, and if it lasts for hours it may produce paralysis,⁶⁵ thrombosis or other serious effects.

- 3 If a series of plethysmographic curves is taken in which the periods of occlusion are constant and equal to the intervening intervals, the individual curves are identical in form. (Only five successive curves were reported.)

- 4 Arterial reactive hyperemia following an occlusion lasting ten minutes produces a greater effect than soaking the arm in water at 43 to 44 C for thirty minutes. (As has been pointed out in this article, direct heat does not produce as great an increase in blood flow as does reflex heat¹⁹.)

- 5 Exercise, according to comparative studies, produces an increase in blood flow which is greater in volume and duration than that pro-

⁶⁵ von Volkmann, R., in Pitha, F. J., and Billroth, T. *Handbuch der allgemeinen und speciellen Chirurgie*, Stuttgart, Ferdinand Enke, 1882, vol. 2, pt. 2A, p. 846.

duced by reactive hyperemia. In reactive hyperemia all the soft tissues seem to be affected, while in exercise the effect is mostly confined to the muscles.

In relation to *venous* reactive hyperemia the authors concluded

- 1 When occlusion of the venous return flow is produced, the venous pressure, within certain limits and with slight variations, rises to equal the cuff pressure.

- 2 When the pressure is 40 to 50 mm of mercury for two minutes or more the pulse volume begins to increase, this becomes maximal in ten to fifteen minutes.

- 3 When a pressure of 20 to 30 mm of mercury in the cuff is released the plethysmographic curve is that of a simple drop to the base line as the veins empty themselves.

- 4 If the cuff pressure has been higher (40 to 60 mm of mercury) the descent of the curve is broken by a hesitation, or a secondary "hump" and reactive hyperemia occurs.

- 5 The size of this "hump," within certain limits, is increased by (a) increasing the cuff pressure, (b) maintaining the cuff pressure for longer periods and (c) raising the temperature.

- 6 This "hump" is in all probability produced by superimposed arterial active dilation and filling to a point at which the arterial blood is entering the limb more rapidly than the veins are emptying.

- 7 Obliteration of the major artery supplying the limb will obliterate the hump.

- 8 Venous congestion carried to a high point (a pressure of 70 mm of mercury) for five to ten minutes seems to yield a curve of vasodilatation not dissimilar in amplitude and duration to that produced by a somewhat shorter period of arterial occlusion.

- 9 The release of venous congestion in a normal limb is followed by flush displacing the cyanosis and varying in duration with the degree and duration of the previous congestion.

"The phenomenon of reactive hyperemia is related in its degree to one factor—namely, to the blood flow debt which is usually a product of the amount by which flow is reduced and the time over which the reduction has been maintained."

The hyperemia results from active dilation of those vessels which are responsible for the color of the skin, namely the arterioles, capillaries and venules. As has been stated, the mechanism is extremely complex, the nervous reaction theory appears untenable. Other factors, including oxygen deficiency and accumulation of carbon dioxide or of other metabolites, such as pituitary hormones have been studied, without conclusive results.

The problem of possible therapeutic application of these principles has been emphasized by Bieri and more recently by Collens and Wilensky,⁶⁶ who have developed an "intermittent venous hyperemia machine" which is capable of reproducing a cycle with the pressure and timing believed desirable.

Several questions must be considered carefully in this regard. Since the phenomenon of reactive hyperemia depends on and is related directly to a preceding "blood flow debt" accumulated during the period of occlusion, is it beneficial or dangerous to tissues which are barely receiving enough nourishment for life to go through periods of increased nutritional debt, even though the hyperemia may compensate later?

If the response of normal persons to arterial reactive hyperemia is much more satisfactory than that to venous reactive hyperemia, should not production of the former be theoretically the technic of choice?

What is the relation of the experiment of Lewis and Grant (in which, by pressure occlusion of the subclavian artery the reactive venous hyperemia was abolished) to arterial obliterative vascular disease and this type of therapy? After repetition of this phenomenon a great many times, does a fatigue syndrome set in, affecting the reaction?

These and many other questions must be answered before the theoretic conclusions are accepted as satisfactory. Veal and McCord⁶⁷ have studied the effects of complete arterial occlusion and intermittent venous occlusion on the oxygen content of the blood with the following results. After complete arterial occlusion of the arm for five to eight minutes followed by release, the oxygen saturation of the blood from the ante-cubital vein showed a definite rise in one minute in 9 of 11 cases. The saturation then decreased at varying rates. After intermittent venous occlusion, however, the tendency was reversed. In 8 of 11 cases there was a definite decrease in oxygen saturation of the blood at the end of one minute after release of the compression. There was no significant change at the end of three minutes. This raises the question whether by "using the cycle 2 2 or 2 1 minutes" and the compression recommended (25 to 80 mm of mercury) true reactive hyperemia is produced. Perhaps the fatigue phenomenon previously mentioned

66 Collens, W. S., and Wilensky, N. D. (a) The Treatment of Peripheral Obliterative Arterial Diseases by the Use of Intermittent Venous Occlusion, *J. A. M. A.* **107** 1960 (Dec 12) 1938, (b) Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, *Am. Heart J.* **11** 705 (June) 1936, (c) An Apparatus for the Production of Intermittent Venous Occlusion, *ibid.* **11** 721 (June) 1936, (d) *Peripheral Vascular Diseases*, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

67 Veal, J. R., and McCord, W. M. Blood Oxygen Changes Following Intermittent Venous Occlusion, *Am. Heart J.* **17** 401 (April) 1939.

entered into these studies. This possibility is not mentioned. Allen and McKechnie⁶⁸ studied the effect of intermittent venous occlusion on the cutaneous temperature under controlled conditions. In 19 patients (9 normal subjects and 10 persons with hypertension, arthritis and peripheral vascular disease) they found no evidence that any significant or consistent vasodilatation resulted from the procedure.

Clinical evaluation of either Bier's hyperemia or intermittent venous hyperemia is extremely difficult. It appears that Bier's hyperemia has been largely abandoned in the United States, either because of lack of conclusive therapeutic results or because new methods seem to offer greater promise. I have never been impressed with the clinical results of this technic in the treatment of arteriosclerosis obliterans or thromboangitis obliterans and have long since ceased to use it.

The status of intermittent venous hyperemia must, in all fairness, be considered as not definitely established. Collens and Wilensky have repeatedly reported excellent results as following its use, but many of their patients were also treated with a regular "vascular regimen" involving abstinence from smoking, warmth and rest (in certain cases), and these factors confuse the picture somewhat. de Takats, Hick and Coulter⁶⁹ reported favorably on the use of this technic in a series of 10 cases, but their conclusions were weakened by the fact that other treatments were used simultaneously, and their series was too small to permit the drawing of any positive conclusions.

Kramer,⁷⁰ Brown and Arnott⁷¹ and Wilson and Ogston⁷² have also reported favorably on this technic.

In the vascular disease clinic and in the wards of the New York Post-Graduate Medical School and Hospital we studied and used this apparatus in 23 cases over a period of about one year. Occlusive conditions of varying severity were used—some advanced and severe, with gangrene, others early and less severe, without gangrene. In

68 Allen, E. V., and McKechnie, R. E., Jr. Effect of Intermittent Venous Occlusion on the Circulation of the Extremities. Studies of Skin Temperature, *J. Lab. & Clin. Med.* **22** 1260 (Sept.) 1937.

69 de Takats, G., Hick, F. K., and Coulter, J. S. Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, *J. A. M. A.* **108** 1951 (June 5) 1937.

70 Kramer, D. W. Periodic or Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, *M. Rec.* **147** 99 (Feb. 2) 1938.

71 Brown, J. J. M., and Arnott, W. M. Intermittent Venous Occlusion in the Treatment of Obliterative Vascular Disease, *Brit. M. J.* **1** 1106 (May 29) 1937, Treatment of Obliterative Vascular Disease by Intermittent Venous Occlusion. Further Observations, *ibid.* **1** 616 (March 19) 1938.

72 Wilson, C., and Ogston, A. G. Treatment of Peripheral Vascular Disease by Intermittent Venous Occlusion. New, Simple and Inexpensive Method. *Lancet* **1** 606 (March 12) 1938.

some instances the cuff was active on the patient practically continuously for as long as six weeks, so that it cannot be charged that it was not given a satisfactory opportunity to demonstrate its worth. We are perfectly willing to admit the difficulty of attempting to evaluate the effects of any therapy on the course of such conditions, but the members of our clinic were unconvinced of the value of the method, and in some instances it was felt to have been harmful. It was therefore discontinued as a routine measure.

Certain contraindications for its use became apparent: (1) a level of arterial blockage above the level of the cuff, (2) active and spreading infection of the wound, especially with streptococci or anaerobic bacteria, (3) extreme toxicity of the patient, and (4) increased pain with the use of the machine. (Collens and Wilensky suggested using a 25 mm pressure in certain cases. Lewis and Grant have shown that reactive venous hyperemia probably does not occur to any appreciable amount at this pressure.)

For most cases a compression of 60 mm of mercury and a cycle of two minutes "on" and two minutes "off" is optimal. The treatment may last from one hour to several months if the patient tolerates it well. Reflex heat, as previously described, is advisable but I do not advise the use of short wave therapy or diathermy for the involved foot as suggested by Collens and Wilensky.^{66a}

This treatment appears indicated largely for arteriosclerosis obliterans and to a lesser degree for thromboangitis obliterans, but the cases must be carefully selected.

COMMENT AND SUMMARY

An attempt has been made to review and evaluate the more important of the methods used in conservative treatment of occlusive peripheral vascular disease, especially arteriosclerosis obliterans and thromboangitis obliterans. The more general use of the conservative approach definitely affects the statistics on amputations. It should be recognized that it is far better surgery to take meticulous care of small lesions and produce healing than to perform major amputations. In a series of 100 consecutive cases of thromboangitis obliterans⁷³ studied since 1931 by Littauer and me only 3 major amputations were performed, all on persons who would not stop smoking. Most of the patients have been followed for two to eight years. The incidence of amputation in this group may be expected to rise with the trauma and other factors incident to the passage of time, but it is extremely doubtful

⁷³ Wright, I. S., and Littauer, D. An Analysis of the Results of Conservative Therapy in One Hundred Cases of Thrombo-Angitis Obliterans, to be published.

that the former amputation rate of 40 to 50 per cent will again be observed. For arteriosclerosis obliterans our figures are not so encouraging. We have not yet compiled statistics on this condition, but we have been impressed by its more hesitant response to therapy. On the other hand, an increasing number of patients who have been advised to submit to amputation are today walking on the condemned leg as a result of conservative therapy. Continued study may result in greater success in this regard. Amputation must be regarded as an admission of defeat, an acknowledgment of the physician's inability to solve the problem with which he is confronted.

It is important that the recent trend in certain quarters toward submitting all patients with vascular disease to the same form of therapy, whether it be use of the pressure suction boot, administration of hypertonic saline solution or intravenous administration of typhoid vaccine, be discouraged. The problems presented by different diseases and by different patients with the same disease are more frequently unlike than identical. Each should be given individual consideration before the therapeutic regimen is instituted. It is also of vital importance that the conception that peripheral vascular disease is purely local, involving only the extremities, be overcome. Each patient should be submitted to a complete study in order that evidences of vascular damage anywhere in the body may be discovered and proper therapy instituted. For example, it is not yet generally recognized that thromboangitis obliterans may affect any artery in the body.

This whole field is just beginning to "open up." New studies are constantly being reported which modify the current conceptions. I am deeply conscious of the limitations of such a review as this. Another decade will no doubt clarify many of the issues raised in this symposium.

THROMBOANGIITIS OBLITERANS

TREATMENT WITH SODIUM TETRATHIONATE AND SODIUM THIOSULFATE

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AND

M R FREELAND, PH D

CHICAGO

Thromboangitis obliterans is a clinical and pathologic entity characterized by peripheral arterial thromboses of obscure origin¹ On the basis of our investigative work, we have concluded that thromboangitis obliterans in the majority of our cases is associated with the following factors (1) changes in the blood, (2) disturbed tissue metabolism, (3) arterial and venous thromboses, which occur most frequently in the peripheral vessels but may occur in any part of the body, and (4) local infection in the involved extremity Until the complex adjustments which compensate for pathologic conditions of the blood are better understood, it will be difficult to detect the disease before serious circulatory deficiency results from arterial thrombosis Infection, infarcts or gangrene frequently directs attention to the circulatory disease

Various changes in the blood have been reported since Koga² first, in 1913, reported increased viscosity In cases of acute involvement we have reported increased viscosity of the blood, rapid sedimentation of the cells, rapid coagulation, increased alkalinity and arterial-like oxygen saturation of the superficial venous blood from the involved extremity³ In improved or recovered patients with thromboangitis obliterans and in patients with other peripheral circulatory diseases these conditions

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1 (a) Homans, J A Text Book of Surgery, Springfield, Ill, Charles C Thomas, Publisher, 1931 (b) Buerger, L Circulatory Disturbances of the Extremities, Philadelphia, W B Saunders Company, 1924

2 Koga, G Treatment of Spontaneous Gangrene of the Extremities, Deutsche Ztschr f Chir **121** 371-382 (Feb) 1913

3 Theis, F V, and Freeland, M R The Blood in Thrombo-Angitis Obliterans, Arch Surg **38** 191-205 (Feb) 1939

of the blood were not present. These findings indicated that there is a relation between the stage of the disease and the complex factors of the pathologic physiology of the blood. To evaluate the importance of changes in the blood, observations should be made while thromboses are forming and during the acute stage of the disease.

Our study of the blood in thromboangitis obliterans included an investigation of the changes produced by smoking. We reported ⁴ that smoking by patients with thromboangitis obliterans generally results in decreased peripheral cutaneous temperatures, increased pulse rate, elevated blood pressure, decreased oxygen saturation of the arterial blood, decreased oxygen saturation of the venous blood in patients with acute thromboangitis obliterans and increased oxygen saturation in the improved patients and in normal controls. Most of the responses seem to be physiologic protective adjustments to reduced oxygen saturation of the arterial blood. Failure of compensatory adjustment to heavy smoking in some persons may be a cause of thromboangitis obliterans leading to thrombosis.

Maddock and Coller ⁵ reported that nicotine is the important ingredient of tobacco and that the deleterious effect of smoking is due to the pharmacologic action of nicotine on the peripheral sympathetic nerves. On the contrary, we found that the specific action of smoking is not entirely on the sympathetic nerves. We observed a decline in temperature of 4 degrees (C) on the sympathectomized fingers after smoking in a case of Raynaud's disease. Similar response to epinephrine was observed on sympathectomized extremities in cases of Raynaud's disease by Smithwick, Freeman and White ⁶. These observations suggest that the effect of smoking on the pulse, blood pressure and peripheral temperatures is due to substances in the circulating blood in addition to sympathetic vasomotor stimulation of the peripheral vessels.

In the treatment of thromboangitis obliterans we have had considerable clinical success with sodium tetrathionate ($\text{Na}_2\text{S}_4\text{O}_6 \cdot \text{H}_2\text{O}$) ⁷ and sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$). This treatment was directed

4 Theis, F. V., and Freeland, M. R. Smoking and Thrombo-Angitis Obliterans, *Ann Surg*, to be published.

5 Maddock, W. G., and Coller, F. A. Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angitis Obliterans, *Ann Surg* 98 70-81 (July) 1933.

6 Smithwick, R. H., Freeman, N. E. and White, J. C. Effect of Epinephrine on the Sympathectomized Human Extremity. An Additional Cause of Failure of Operation for Raynaud's Disease, *Arch Surg* 29 759-767 (Nov.) 1934.

7 Sodium tetrathionate has been prepared for us experimentally and supplied by G. D. Searle and Company, of Chicago.

toward improvement of the condition of the blood. The following facts seem pertinent: 1 Pathologic changes in the blood are present during the acute stage of the disease. 2 Clinically, smoking is associated with an acute attack of the disease, and we believe that heavy smoking may contribute to the changes in the blood. 3 Sodium tetrathionate and sodium thiosulfate are of clinical value in the treatment of the disease. We are reporting the results of our investigation of the effect of these solutions on various changes in the blood and physiologic responses which are affected by smoking. The two solutions are referred to as the inorganic sulfur compounds.



Fig 1—Patient with thromboangitis obliterans. The blood picture in his case is given in table 2. The left leg was amputated in 1935. There was recurrence of the disease in the right foot in 1936.

METHOD OF INVESTIGATION

The methods of obtaining peripheral temperatures, pulse rate and blood pressure and of collecting and analyzing the blood were the same as those used in our previous work.⁸ Determinations of glutathione were made by the method of Woodward and Fry.⁹

8. Theis, F. V., and Freeland, M. R. Peripheral Circulatory Disease. Effect of Alternating Positive and Negative Pressure Treatments on Venous Blood and the Skin Temperatures, *J. A. M. A.* **197**: 1097-1104 (Oct. 7) 1936, footnotes 3 and 4.

9. Woodward, G. E., and Fry, E. G. The Determination of Blood Glutathione, *J. Biol. Chem.* **97**: 465-482 (Aug.) 1932.

After the period of stabilization of the subject at rest in bed and initial observation of peripheral temperatures, pulse rate and blood pressure, specimens of arterial blood from the right radial artery or of venous blood from the right antecubital vein were obtained under oil and immediately transferred to mercury tonometers. Injections of sodium tetrathionate or sodium thiosulfate in 10 cc of triple-distilled water were given in the left antecubital vein, and ten minutes later specimens of blood were again withdrawn from the right side. The various observations mentioned were repeated under the same resting conditions after the injection.

RESULTS

Peripheral Temperatures—The average temperature of the fingers and toes was usually increased after intravenous injection of either solution. Figure 2 shows that the inorganic sulfur compounds had

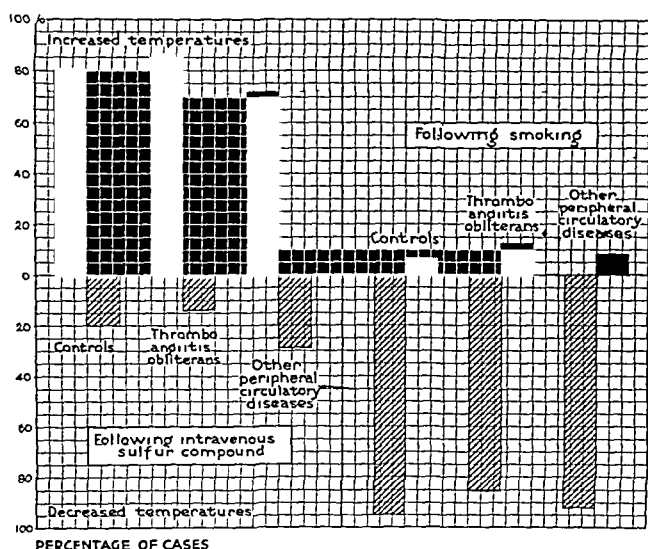


Fig 2—Changes in peripheral temperature of the skin. The inorganic sulfur compounds produced the opposite effect on the temperatures to that which occurred after smoking. Increased temperature is indicated by solid black, decreased temperature, by diagonal lines.

an action that was the opposite of smoking. The more rapid and higher elevations in temperatures were produced by the sodium thiosulfate solution, but the effect was of shorter duration than with sodium tetrathionate. Decreased temperatures were occasionally observed, especially in nervous patients, probably as a result of the puncture.

Cutaneous temperatures were more constantly increased when no element of vasoconstriction was present. In completely sympathectomized extremities or when block of the peripheral nerves with procaine hydrochloride had demonstrated organic circulatory disease, the inorganic sulfur compounds still produced an increase in cutaneous temperature of 0.5 to 1 degree (C). Since vasomotor action was no

longer present in these cases, the increased cutaneous temperatures were produced through the blood stream, probably as a result of increased local tissue metabolism

Blood Pressure—The extent of the reduction in blood pressure which frequently followed injection of inorganic sulfur compounds in patients with thromboangitis obliterans depended on the initial pressure. High initial levels responded with a greater reduction in pressure. In the acute stage of the disease the blood pressure was not elevated, consequently a less marked reduction occurred after injection. The reduction varied from 8 to 40 mm of mercury in different patients and also in the same patient on different days. The diastolic pressure was less affected than was the systolic, although the two were occasionally affected to the same extent.

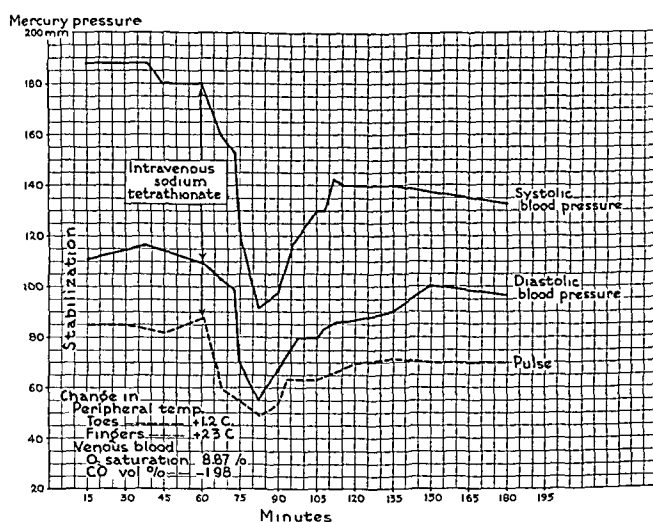


Fig 3—Effect of inorganic sulfur on a patient with essential hypertension and peripheral circulatory symptoms. Marked symptomatic relief accompanied reduction in the systolic and diastolic blood pressures and in the pulse rate after intravenous injections of 0.4 Gm of sodium tetrathionate. Bimonthly and then monthly injections over a period of eighteen months have maintained the subjective and objective improvement.

Hypertension with peripheral circulatory symptoms (fig 3) may be benefited by intravenous injections of the sulfur compounds to the same degree as the circulatory diseases with hypertension, especially when smoking is a cause of the elevated pressure (fig 4). The immediate reduction in pressure which followed injection was almost always transitory, but occasionally with subsequent injections the pressure remained at a lower level. Sodium tetrathionate produced a more constant and longer-lasting effect in lowering the pressure than did sodium thiosulfate.

Pulse Rate—The pulse rate was usually slower after injection of the solutions, especially when the initial rate was higher than normal. With a rate of 80 or 90 per minute, a drop to 70 or less was not uncommon.

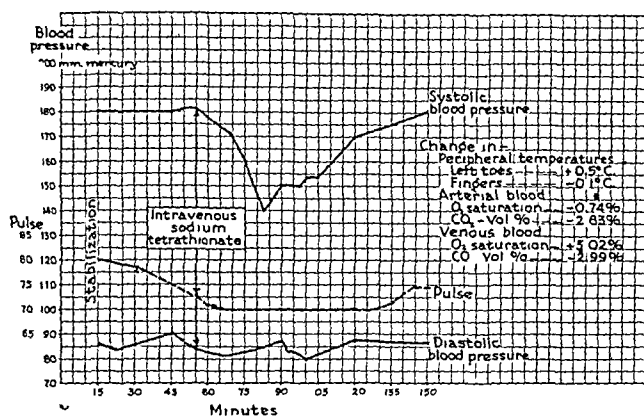


Fig 4—Effect of inorganic sulfur on a clinically well patient with thromboangiitis obliterans and hypertension who continued to smoke two or more packages of cigarets daily. The right leg had been amputated. In addition to the marked reduction in blood pressure and slowing of the pulse rate, insignificant changes occurred in the peripheral temperatures and in the arterial oxygenation after injection of 0.6 Gm of sodium tetrathionate. Clinical improvement has been maintained for four years by biweekly injections, despite heavy smoking.

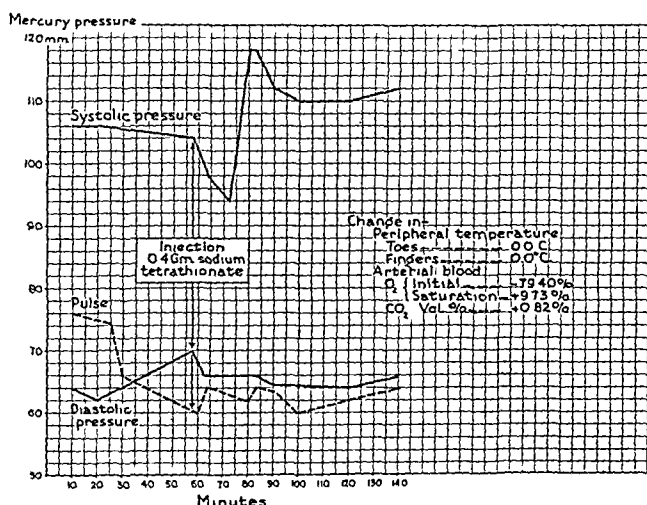


Fig 5—Effect of inorganic sulfur on a patient with Raynaud's disease. The initial oxygen saturation of the arterial blood was 79.40 per cent. Normally, in this vicinity the oxygen saturation is from 92 to 95 per cent. After injection of 0.4 Gm of sodium tetrathionate, elevation of the initial low blood pressure was accompanied by an increase of 9.73 per cent in oxygen saturation of the arterial blood and by a reduction in the pulse rate.

mon The effect of the inorganic sulfur compounds on the pulse rate was of longer duration than its effect on the blood pressure

In 2 cases of Raynaud's disease with initial low oxygenation of the arterial blood and low blood pressure, injection of the tetrathionate solution was followed by elevation of the blood pressure to a normal level, slowing of the pulse and increased oxygen saturation of the arterial

TABLE 1—*Changes in the Oxygen and Carbon Dioxide Content of the Arterial Blood and in the Peripheral Cutaneous Temperatures Ten Minutes After Intravenous Injection of an Inorganic Sulfur Compound*

	Oxygen Capacity, Vols %	Initial Oxygen Saturation, %	Change in Oxygen Saturation, %	Change in Carbon Dioxide, Vols %	Change in Temperature	
					Toes	Fingers
Controls (normal)						
Average for 10 patients	20.24	93.20				
Mr A	20.96	93.91	-2.69	-1.34	-0.9 C *	-0.7 C *
Mr K	18.20	94.40	+1.90	-5.40	-0.6 C *	-0.7 C *
Peripheral circulatory disease (thromboangitis obliterans)						
Mr P	19.16	87.50	+3.85	+0.62	-0.4 C	+1.5 C
Mr S	16.86	91.89	+2.25	-2.13	+0.2 C	+0.2 C
Mr K 7/27/39	11.00	96.10	-8.70	-1.50	+1.3 C	+0.4 C
8/10/39	17.60	96.10	-5.80	-0.80		
Mr Z	11.68	94.00				
Mr B, 6/17/37	20.48	88.14	+1.05	-2.10	+0.4 C	+1.3 C
6/23/37	19.65	93.44	-3.24	-1.85	+1.0 C	+0.6 C
Mr S, 7/ 8/37	19.95	87.80	+1.30	-0.02		
11/29/37	17.74	88.20	+0.80	-0.88	+0.2 C	-0.2 C
Mr H	19.98	80.34	+3.82	-1.86	-1.2 C	
Mr P	17.71	94.82	-0.74	-2.83	+0.5 C	
Mr M	16.30	91.22	-1.58	-1.54	+0.5 C	+0.2 C
Mr B, 4/19/39	14.29	81.20				
7/22/39	20.00	91.40	+2.80	+0.05	+1.4 C	+0.6 C
Raynaud's disease						
Miss J, 2/9/39	16.64	79.40	+9.73	+0.82	0.0 C *	0.0 C *
6/8/39	16.68	93.00	+0.80	-0.20	0.0 C	0.0 C
Miss P	17.36	82.90	+14.00	+1.51	0.0 C	-0.5 C
Miss B	17.04	95.50	+0.30	-0.59	0.0 C	+2.0 C
Mrs W	16.80	84.60	+6.50		-0.9 C	+3.2 C
Senile arteriosclerosis						
Mr T	15.75	98.65	-4.91	-0.70	+3.7 C	+0.2 C
Mr R		91.64	+0.32		-2.5 C	-0.3 C
Unclassified conditions						
Mr De	14.72	89.39	+2.29	-1.05	+0.6 C	-1.2 C
Mr S	19.00	95.04	-2.21	+0.96	+3.5 C	+0.8 C
Mr D	18.80	88.60	+4.90	+0.90		
Mr S	20.00	83.90	+14.80		-0.9 C	0.0 C

* Decreased peripheral temperatures usually occurred in nervous patients when difficulty was encountered in performing arteriopuncture

blood (fig 5) This indicates a relation between the physiologic mechanism of blood pressure, the pulse rate and the oxygenation of the arterial blood

Arterial Blood—The oxygen capacity of normal arterial blood is from 19 to 21 volumes per cent in males and from 17 to 19 volumes per cent in females In patients with thromboangitis obliterans the capacity varied from 11 to 20 volumes per cent (table 1) Two patients had an oxygen capacity of only 11 volumes per cent without a reduc

tion in the erythrocyte count and the hemoglobin index to account for the low capacity. The venous blood of another patient (no arterial blood obtained) had an oxygen capacity of 10 volumes per cent (table 2)

TABLE 2—*Effect of Sodium Thiosulfate or Sodium Tetrathionate on Blood Withdrawn from the Right Cubital Vein Ten Minutes After Injection in Left Cubital Vein in a Case of Thromboangitis Obliterans**

	Oxygen Capacity, Vols %	Content of		Oxygen Saturation, %	Percentage of Hemoglobin and Blood Counts per Cu Mm	Changes in Temperature	
		Oxygen, Vols %	Carbon Dioxide, Vols %			Toes	Fingers
6/29/36 sodium thiosulfate, 2 Gm new case no previous treatment							
Before injection	10.31	7.61	45.58	73.82	Hb 78		
After injection	17.42	17.13	39.31	98.40	R B C 4,080,000		
Change	+7.11	+9.52	-6.27	+24.58	W B C 8,900		
7/2/36 three days of sodium thiosulfate (2 Gm)							
Before injection	10.08	6.81	52.02	67.60	Hb 70		
After injection	14.70	12.30	45.37	83.67	R B C 3,950,000		
Change	+4.62	+5.49	-6.65	+16.07	W B C 9,900		
12/10/36 no treatment for 5 months, improved but still has continuous rest pains							
Before injection (arm)	14.11	9.42	36.82	66.77	R B C 4,100,000		
10 min later (repeat)		9.28	46.87	65.76			
After injection	13.32	10.50	45.06	78.80	R B C 3,680,000		
Change	-0.79	+1.08	-1.76	+12.03			+0.4
Before injection (leg)	15.22	5.13	47.02	33.70	R B C 3,970,000		
After injection	14.25	6.0	49.27	42.38	R B C 3,550,000		
Change	-1.06	+0.97	+2.25	+8.58			-0.8
Coagulation time, 1¼ min							
Sedimentation time, 16 min							
12/23/36 two weeks daily treatment, sodium thiosulfate 2 Gm daily							
Before injection	15.10	12.02	39.55	79.60	R B C 3,570,000		
After injection	15.17	12.05	39.10	79.60	R B C 3,770,000		
Change	+0.07	+0.06	-0.40	0.00		+0.1	+0.8
1/6/37 sodium thiosulfate, 2 Gm daily marked clinical improvement no pain							
Before injection	15.27	8.18	51.37	53.60			
After injection	15.25	10.46	47.88	68.60			
Change	-0.02	+2.28	-3.49	+15.00		+0.3	+1.3
4/1/37 improving no treatment for four months							
Before injection	16.62	9.01	48.81	54.02	R B C 4,070,000		
After injection	16.62	9.75	46.02	58.65	R B C 4,800,000		
Change	0.00	+0.74	-2.79	+4.63		+0.8	+1.0
pH before, 7.495							
pH after, 7.548							
1/13/38 injection of 0.6 Gm sodium tetrathionate no pain improving no treatment since April 1, 1937							
Before injection (arm)	15.78	12.08	37.64	76.54	R B C 3,930,000		
After injection	15.50	8.80	38.02	56.45	R B C 4,110,000		
Change	-0.19	-3.28	+0.38	-20.11		-0.9	+0.5
Before injection (leg)	15.02	4.62	41.50	70.77	R B C 3,160,000		
Sedimentation time 15 min							

* There was an acute recurrence of the condition in the left foot. The right leg had been amputated (fig. 1).

The exceptionally low oxygen capacity in such patients may be due to some unknown ingredient of the dark blood which interferes with the analytic reagents or to some inactive form of hemoglobin. Spectroscopic and quantitative chemical tests have not revealed the presence of significant amounts of methemoglobin and carboxyhemoglobin.²

The oxygen saturation of normal arterial blood in this locality is from 92 to 95 per cent. In cases of thromboangitis obliterans as well as of Raynaud's disease the oxygen saturation was found to be as low as 80 per cent. In cases with unusually low oxygen capacity, normal oxygen saturation was noted. Low blood pressure, especially in the presence of Raynaud's disease, may contribute to the low oxygen saturation of the arterial blood.

Treatment in these cases with sodium tetrathionate or sodium thio sulfate was usually followed by return of more nearly normal oxygen

TABLE 3—*Changes in Oxygen Saturation of the Venous Blood After Injection of an Inorganic Sulfur Compound*

	No of Patients Examined	Percentage of Oxygen Saturation							
		Increase				Decrease			
		No of Tests	Maximum	Minimum	Average	No of Tests	Maximum	Minimum	Average
Normal controls	11	2	9.46	3.26	6.36	9	15.27	0.5	0.0
Patients with peripheral circulatory disease									
Thromboangitis obliterans	20	38	34.10	0.02	9.44	10	21.76	0.6	9.08
Neurocirculatory disease	7	4	32.94	6.2	14.18	5	6.34	1.26	3.94
Patients with polycythaemia vera (not thromboangitis obliterans)	2	2	10.4	3.9	7.10	0			
Patients with arteriosclerosis									
Senile	2	2	5.4	1.8	3.6	0			
Diabetic	1	0				1	19.75		
Patients with frostbite	1	0				1	6.3		
Patients with thrombophlebitis									
Acute	1	1	2.1			0			
Recovered	2	0				2	9.81	5.17	7.49

capacity, saturation of the arterial blood, blood pressure and pulse rate. Clinical improvement accompanied these changes.

Venous Blood—After injection of the inorganic sulfur compounds the oxygen saturation of the venous blood was decreased in 81 per cent of the normal controls and increased in 79 per cent of patients with thromboangitis obliterans (table 3). A similar increase in oxygen saturation occurred in 2 cases of Raynaud's disease. The fact that the change in oxygen saturation of the venous blood of patients with thromboangitis obliterans was opposite to that which occurred in the normal controls is significant. The increased peripheral temperatures and the accompanying changes in the venous blood were the reverse of those which occurred after smoking (figs 2 and 6).

The oxygen capacity of the venous blood of some patients (table 2) with thromboangiitis obliterans was increased after injection of the inorganic sulfur compounds. This has been discussed in connection with the arterial blood and was not due to changes in the erythrocyte counts and hemoglobin content. Since colorimetric hemoglobin standards are based on oxygen capacity, the aforementioned changes in the oxygen capacity of the dark arterial and the venous blood suggested activation of some inactive hemoglobin by the sulfur compounds.¹⁰ An increase in glutathione, which is a sulfur-containing oxidation catalyst, may contribute to this action. The catalyst may be deficient in any of the body tissues, but its deficiency in the blood would be reflected throughout the body.

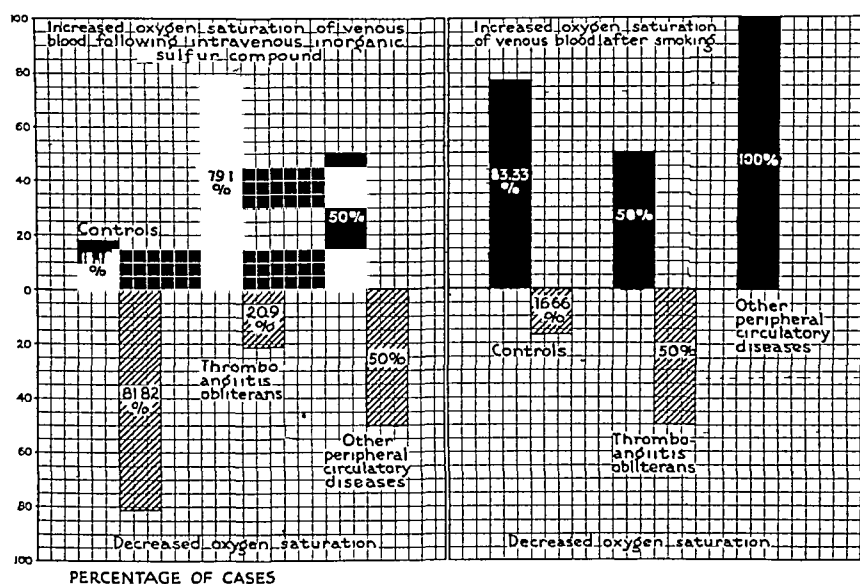


Fig 6—Changes in oxygen saturation of the venous blood from the right antecubital vein. Note the opposite effect of the inorganic sulfur to that of smoking.

Glutathione—The utilization of oxygen by the tissues has been shown to be partly under the control of an oxidation catalyst, glutathione. This substance is found in the blood in two forms, the reduced, active form and the oxidized, inactive form. The results of our study of the glutathione content of the venous blood are contained in table 4. The average content for the normal controls and for patients with arteriosclerotic disease was practically the same.

10 Ammundsen, E. The Presence of Non-Oxygen-Combining (Inactive) Hemoglobin in the Blood of Normal Individuals, *Science* 90:372-373 (Oct 20) 1939.

In 2 cases of acute thromboangitis obliterans we found an unusually low content of the reduced form of the catalyst and a high content of the oxidized form. After intensive treatment with the inorganic sulfur

TABLE 4—*Glutathione Content of the Venous Blood. Effect of Sodium Tetrathionate and Sodium Thiosulfate on Untreated and Treated Thromboangitis Obliterans and Other Peripheral Circulatory Diseases*

	No of Patients	No of Tests	Glutathione Mg /100 Cc			Comment
			Total	Reduced	Oxidized	
Controls						
Maximum			69.0	44.6	34.4	
Minimum			39.4	25.5	13.9	
Average	8	10	58.23	38.28	21.04	Normal
Peripheral Circulatory Diseases						
Thromboangitis obliterans						
Acute						
Mr. E. New case no gangrene or infection						
8/20			69.5	12.7	56.8	No treatment
8/27 Injection of 0.6 Gm. sodium tetrathionate						
Before injection			61.4	11.7	49.7	
After injection			61.3	12.7	48.6	
9/24 Injection of 1 Gm. sodium thiosulfate						
Before injection			83.8	52.6	31.2	Treated 4 weeks
After injection			79.8	56.6	23.2	improved
Mr. M. Both legs involved previously, hands involved now						
8/30 Injection of 0.6 Gm. sodium tetrathionate						Recurrence
Before injection			61.4	18.1	43.3	
After injection			47.5	17.0	30.5	
9/10 Injection of 1 Gm. sodium thiosulfate						
Before injection			61.3	50.0	11.3	Intensive treatment
After injection			71.4	54.1	17.3	
Mr. S.						
9/9 Injection of 0.4 Gm. sodium tetrathionate						Intensive treatment
Before injection			61.30	38.28	23.02	two months
After injection			61.40	38.20	23.20	improved
11/15 Injection of 1 Gm. sodium thiosulfate						Serious infection
Before injection			53.8	30.8	23.0	developed on calf
After injection			52.4	36.8	15.6	of leg
11/26 Injection of 0.6 Gm. sodium tetrathionate						
Before injection			48.9	34.6	14.3	
After injection			55.2	37.3	17.9	
11/29 Injection of 0.6 Gm. sodium tetrathionate						Infection clearing
Before injection			52.1	34.5	17.6	up
After injection			56.2	34.8	21.4	
Improved or recovered						
Maximum			83.8	52.6	31.2	
Minimum			37.0	20.1	16.9	
Average	15	30	50.11	33.57	16.54	
Raynaud's disease						
Maximum			52.0	29.5	22.5	
Minimum			34.4	11.9	22.5	
Average	3	6	38.77	24.80	13.97	
Senile arteriosclerosis						
Maximum			69.0	44.6	24.4	
Minimum			58.6	36.6	22.0	
Average	5	5	61.50	40.68	20.82	

compounds the reduced glutathione as well as the oxidized substance was frequently increased above normal levels. In Raynaud's disease both the reduced and the oxidized form were below normal levels. One patient with Raynaud's disease had an initial reduced glutathione

content of 11 mg per hundred cubic centimeters of blood, which was the low level found in cases of thromboangitis obliterans. The clinical similarity between Raynaud's disease in females and thromboangitis obliterans in males is occasionally observed¹¹

Direct Action of the Sulfur Compounds on the Blood—Oxygen and carbon dioxide determinations for the venous blood were made before and after addition of a few crystals of the chemical to the blood. The oxygen capacity and content thus examined in vitro were unaffected, but the carbon dioxide content was reduced. In vivo, however, the small amount of the sodium solutions injected intravenously would be insignificant in reducing the carbon dioxide content of approximately 6 quarts of blood.

Reaction of the Blood—The actual and the theoretic p_H of the blood were frequently increased temporarily by the injection of the sulfur compounds. A rapid increase in p_H from 7.42 to 7.52 as observed in 1 clinically recovered patient with thromboangitis obliterans could not have been due to the action of the small amount of sodium in the solution in reducing the carbon dioxide content of the blood. Changes in the oxyhemoglobin could be reflected in a shift of hydrogen ion concentration. Activation of some form of inactive oxyhemoglobin would contribute to this effect¹². The high p_H (7.60 or more) which we reported for patients in the acute stage of thromboangitis obliterans was found to be reduced to normal levels after intensive treatment with the inorganic sulfur compounds.

Blood Counts—The immediate effect of the inorganic sulfur compounds on the erythrocyte counts was studied in 30 cases. The results showed no constant change. Polycythemic counts, however, returned to normal after intensive treatment. The high erythrocyte counts and hemoglobin values were probably compensatory adjustments for a deficiency in available oxygen¹³.

Erythrocyte Counts per Cubic Millimeter of Blood (30 Patients)

	Maximum	Minimum	Average
Before injection	5,640,000	3,680,000	4,830,000
After injection	5,850,000	3,570,000	4,776,000

11 Reid, M. R. The General Care of Peripheral Vascular Diseases, *Ann Surg* **96** 733-743 (Oct.) 1932. Homans^{1a}

12 Litarczek, G., Aubert, H., and Cosmulesco, I. Studies on the Mechanism of the Reaction of Glutathione on the Dissociation Curve of Oxyhemoglobin. *Compt rend Soc de biol* **109** 781-783, 1932.

13 Barcroft, J. The Respiratory Function of the Blood. I. Lessons from High Altitudes, London, Cambridge University Press 1925.

Excretion of Sulfate in the Urine—Thiosulfate is rapidly oxidized in the body and largely excreted in the urine as sulfate Holbøll¹⁴ reported that 60 to 70 per cent is thus eliminated, and Walko¹⁵ found 50 to 70 per cent in the urine This rapid elimination offers an expla-

TABLE 5—*Effect of Intravenous Injections of Sodium Thiosulfate and Sodium Tetrathionate on Excretion of Sulfates in the Urine*

		Urine Volume, Cc	Inorganic Sulfates	Total Sulfates
Twenty Four Hour Specimens				
Controls				
Mr M	No injection	1,400	1 0556	1 1392
Mr O	No injection	1,000	1 2480	1 3420
Composite specimen (aver of 12 patients, no injection)		2,674	1 2937	1 3389
Mr V				
5/18/37	No injection	510	0 6100	0 6793
5/19/37	2 Gm sodium thiosulfate	610	1 8909	1 9104
5/20/37	0 885 Gm sodium tetrathionate	300	0 5112	0 5708
Thromboangitis obliterans				
Mr N				
4/28/37	0 885 Gm sodium tetrathionate	1 400	1 5344	1 8038
4/29/37	No injections smoking cigaret	2,200	1 392	1 7248
4/30/37	2 Gm sodium thiosulfate	2 500	2 1800	2 380
5/1 37	No injection no smoking	3,500	1 5820	1 7150
Mr B				
6/16/37	No injection	2,100		2 150
6/17/37	2 Gm sodium thiosulfate	3,425		3 226
6/20/37	2 Gm sodium thiosulfate	3,350		3 702
6/23/37	0 885 Gm sodium tetrathionate	3,375		3 6967
6/24/37	2 amp of 0 885 Gm sodium tetrathionate	2,275		3 1800
Individual Specimens				
Thromboangitis obliterans				
Mr M 5/20/37 0 885 Gm sodium tetrathionate				
	Before injection	270	0 0292	0 0443
	After injection, ½ hour	285	0 0410	0 0467
	2½ hours	465	0 1711	0 2362
Mr N 5/4/37 1 Gm sodium thiosulfate				
	Before injection	50	0 0370	0 0672
	After injection 1 hour	50	0 2174	0 232
5/8/37 1 Gm sodium thiosulfate				
	Before injection	50	0 0804	0 0832
	After injection, 1 hour	75	0 2361	0 2463
	1½ hours	250	0 1060	0 1150
	2 hours	300	0 0996	0 1005
5/12/37 0 885 Gm sodium tetrathionate				
	Before injection	50	0 0834	0 0922
	After injection, 1½ hours	50	0 2480	0 2726
	3 hours	50	0 2300	0 2024
5/13/37 0 885 Gm sodium tetrathionate				
	Before injection	77	0 1029	0 1141
	After injection, 2 hours	68	0 3370	0 3467
Mr B 5/20/37 2 Gm sodium thiosulfate				
	Before injection	315	0 1551	0 1915
	After injection, ¾ hour	135	0 2084	0 2392
	2½ hours	285	0 1915	0 2383

* One gram of the thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3 \cdot 5 \text{H}_2\text{O}$) contains 0 258 Gm of sulfur, and 0 885 Gm sodium tetrathionate ($\text{Na}_2\text{S}_4\text{O}_6 \cdot \text{H}_2\text{O}$) contains 0 393 Gm of sulfur

nation for the transitory effect of the thiosulfate solution on the peripheral temperatures, pulse rate and blood pressure

14 Holbøll, S A Quantitative Determinations of Sodium Thiosulphate in the Urine, Klin Wchnschr 4 1636-1640 (Aug 20) 1925

15 Walko, K Concerning the Removal of Poisons by Oxidizing Agents, Arch internat de pharmacodyn 4 311-323, 1897-1898

At the suggestion of William D McNally, of the department of toxicology, we had prepared for us sodium tetrathionate ($\text{Na}_2\text{S}_4\text{O}_6 \cdot \text{H}_2\text{O}$), which he had found to be more beneficial than sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$) in cases of metallic poisoning. The intravenous dose (1 Gm) of sodium thiosulfate contained 0.258 Gm of sulfur, and the 0.885 Gm of sodium tetrathionate injected contained 0.393 Gm of sulfur. The results of sulfate determinations for the urine are shown in table 5.¹⁶ The entire additional elimination after injection was in the free sulfate.¹⁷ The remainder, present as ethereal sulfate, was apparently unaffected. The volume of urine in individual specimens had no relation to the amount of sulfate eliminated, although the twenty-four hour volume indicated diuresis. No food was taken for at least four hours before the individual specimens were obtained or during the period of collection of subsequent specimens. This prevented changes in the determinations as a result of diet.

Determinations of the sulfate content of the urine immediately before and at varying intervals after injection showed that the thiosulfate solution was more rapidly eliminated than was the tetrathionate. In cases of thromboangitis obliterans the excretion of sulfate in the twenty-four hour specimens was greater than that observed for the normal controls, the composite urine from 12 normal subjects averaged approximately the same for free and total sulfate content as did that from 2 individual patients. The more rapid excretion of the thiosulfate in the urine may account for the fact that the effect of sodium thiosulfate was more transitory than that of sodium tetrathionate.

COMMENT

The peripheral arterial occlusion associated with thromboangitis obliterans is seldom detected until examination for arterial pulsation is made because of infection, infarcts, gangrene or acute circulatory deficiency with impending gangrene. Gross specimens of amputated extremities reveal that the occlusions have been progressive or successive. Although infection has been suspected as the cause of the disease, extensive investigations have failed to establish a bacterial cause. The significance of changes in the blood which disturb tissue metabolism and contribute to thrombosis is difficult to evaluate because of the involved physiologic processes.

16 The determinations of urine sulfate were made by Willard Bergman, assistant to Dr William D McNally.

17 Folin, O. Approximately Complete Analysis of Thirty "Normal" Urines, *Am J Surg* 21: 260-271 (Aug) 1933.

Naftziger and his co-workers¹⁸ at the University of California reported the results of their investigation of the role of sulfur in the hemorrhagic tendency associated with obstructive jaundice. They found that in obstructive jaundice, either in experimental animals or in man, the sulfur content of the venous blood is increased. They contended that certain sulfur compounds retained in the blood act as anticoagulants. Interesting and important contributions on the sulfur-containing anti-coagulant heparin have been made by Best and others¹⁹. The role of heparin in disease conditions and the effect of therapy on the heparin content of the blood cannot be evaluated until quantitative determinations can be made. Unfortunately, no quantitative test²⁰ for heparin is available.

To the best of our knowledge, sodium thiosulfate was first used empirically in the treatment of thromboangitis obliterans by Dr. Robert Johanneson, of the Presbyterian Hospital in Chicago. Although a few striking results were obtained, there was no information as to the modus operandi of the therapy or to the means of selecting patients who may be benefited. Rabinowitz²¹ in 1933 and Rabinowitz and Kahn²² in 1936 reported the presence of abnormal phospholipin metabolism and its effect on utilization of oxygen by the tissues. They were the first to report the use of sodium thiosulfate for thromboangitis obliterans. Additional metabolic changes associated with the disease have been reported by Friedlander and Silbert²³ for cholesterol metabolism and

18 Naftziger, H. C., Carr, J. L., and Foote, F. S. Obstructive Jaundice, *Ann Surg* **106** 745-751 (Oct) 1937.

19 Best, C. H., Charles, A., and Cowan, C. The Administration of Heparin, *Proc Am Physiol Soc* **119** 272-273 (May) 1937. Best, C. H., and Taylor, N. B. The Physiological Basis of Medical Practice, Baltimore, William Wood & Company, 1937. Best, C. H. Heparin and Thrombosis, *Proc Inst Med Chicago* **12** 210-218 (Dec 15) 1938. Murray, D. W. G., Jacques, L. B., Perrett, T. S., and Best, C. H. Heparin and Vascular Occlusion, *Canad M A J* **35** 621-622 (Dec) 1936. Best, C. H. Heparin and Thrombosis, *Proc Staff Meet, Mayo Clin* **14** 81-84 (Feb 8) 1939. Best, C. H., and Murray, D. W. G. Heparin and Thrombosis of Veins Following Injury, *Surgery* **2** 163-187 (Aug) 1937. Best, C. H., Cowan, C., and MacLean, D. I. Heparin and Formation of White Thrombi, *Science* **85** 338-339 (April 2) 1937.

20 Best, C. H. Personal communication to the authors.

21 Rabinowitz, H. M. Thrombo-Angitis Obliterans, *Am J Surg* **21** 260-271 (Aug) 1933, The Use of Sodium Iodide Thiosulphate in the Treatment of Thrombo-Angitis Obliterans, *J Chemotherapy* **13** 1-4 (April) 1936.

22 Rabinowitz, H. W., and Kahn, J. The Relationship of Phospholipin Metabolism to Thrombo-Angitis Obliterans and Its Treatment, *Am J Surg* **31** 329-339 (Feb) 1936.

23 Friedlander, M., and Silbert, S. Thrombo-Angitis Obliterans. VI Chemistry of the Blood, *Arch Int Med* **48** 500-506 (Sept) 1931.

by Bernhard²⁴ for sugar metabolism Roth, Maclay and Allen²⁵ found inconstant changes in serum calcium, serum protein, blood urea, serum lecithin, serum phosphorus, cholesterol and hematocrit values The importance of these observations may be underestimated because of the difficulty in interpreting pathologic blood pictures in different stages of the disease

Bancroft and his associates²⁶ have extensively investigated and reported on the use of sodium thiosulfate for thrombophlebitis The problem studied was directed to determine the effect of sodium thiosulfate on the clotting index of the plasma and the fibrinogen content of the blood, on the assumption that, as there are definite bleeding diatheses, there are also potential "clotters" After using the thiosulfate solution prophylactically for a number of years against postoperative thrombophlebitis, Bancroft concluded that the morbidity may be definitely reduced by injections of sodium thiosulfate combined with a diet low in fats and proteins

The changes in blood pressure, pulse and peripheral temperature seem to influence or to be affected by the available oxygen in the blood The occasional low oxygen saturation (80 per cent) of the arterial blood in cases of thromboangiitis obliterans may be increased to normal with an accompanying elevation in blood pressure and the shunting of the peripheral circulation which follows smoking Subsequently, the oxygen saturation was decreased by continued smoking, and this decrease may have been due to formation of inactive oxyhemoglobin In 2 cases of thromboangiitis obliterans the oxygen capacity was only 11 volumes per cent, with 80 per cent hemoglobin (by the Dare method) and over 4,400,000 erythrocytes per cubic millimeter Without significant changes in the hemoglobin or red cell count the oxygen capacity was increased to more than 17 volumes per cent after treatment with inorganic sulfur compounds The presence of an unidentified form of inactive hemoglobin has just been confirmed by a report from Copenhagen, Denmark¹⁰

24 Bernhard, A Summary of the Chemical Blood Findings in Thrombo-Angiitis Obliterans, *M Rec* **97** 430-431 (March 31) 1920

25 Roth, G M, Maclay, E V, and Allen, E V Blood in Thrombo-Angiitis Obliterans, *Arch Int Med* **6** 413-422 (Sept) 1938

26 Bancroft, F W, Kugelmass, I N, and Stanley-Brown M Evaluation of Blood Clotting Factors in Surgical Diseases, *Ann Surg* **90** 161-189 (Aug) 1929 Bancroft, F W, and Stanley-Brown, M Postoperative Thrombosis Thrombophlebitis and Embolism, *Surg, Gynec & Obst* **54** 898-906 (June) 1932 Bancroft, F W, Stanley-Brown, M, and Quick, A Postoperative Thrombosis and Embolism, *Am J Surg* **28** 648-668 (June) 1933 Bancroft F W, Stanley-Brown, M, and Charnoff, E Postoperative Thrombosis and Embolism, *Ann Surg* **106** 868-879 (Nov) 1937

The reports of investigations on bleeding and thrombotic diseases show a relation between the role of sulfur as used in the thiosulfate or the tetrathionate solution and the tendency to thromboses in cases of thromboangitis obliterans. Further, the inorganic sulfur solutions have the opposite effect on the conditions studied to that of smoking, which is generally accepted as a cause of the disease. The clinical value of the inorganic sulfur solutions may be due to the fact that the effect on blood and tissue metabolism is the opposite to that observed with smoking.

SUMMARY

Sodium tetrathionate and sodium thiosulfate injected intravenously may produce a marked increase in the oxygen capacity and content of the circulating blood in some patients. This was most marked in patients with active thromboangitis obliterans and dark, thick blood, no significant increase in the erythrocyte count or the hemoglobin value for hemoglobin accompanied the change. The presence of an inactive form of oxyhemoglobin seemed most likely to account for this effect.

In accounting for the marked increase in oxygen capacity and content of the blood of some patients after injection of inorganic sulfur, we considered three possibilities: (1) reduction of methemoglobin or of some unidentified form of inactive hemoglobin, (2) additional supply of oxygen in the sulfate (S_2O_3), or (3) increase in the oxidation catalyst, the reduced form of glutathione. We were unable to establish the presence of a known form of inactive hemoglobin, and the small amount of reducing agent was inadequate to produce the marked increase in oxygen in the approximately 6 quarts of blood. By actual determination, the sulfur compounds did not add oxygen to the blood. All evidence seemed to corroborate our findings that a catalytic action was produced by the injected chemical.

Ammundsen²⁰ has just reported from Copenhagen, Denmark, the presence of non-oxygen-containing hemoglobin in normal persons. Activation of this hemoglobin occurred on administration of sodium hydrosulfate. The composition of the pathologic hemoglobin and the cause for its appearance are unknown, but it is not to be assumed that all hemoglobin circulating in the blood is capable of freely combining with oxygen.

Sodium thiosulfate has been found to increase the glutathione in the liver and in the blood.²⁷ Glutathione, a sulfur-containing oxidation catalyst of the blood and tissues, is efficient in reducing methemoglobin,

²⁷ Arnovljjevitich, V. Increase of Glutathione in the Liver and the Blood After Administration of Sodium Thiosulphate, *Compt rend Soc de biol* **106** 681-684, 1931, *Physiol de abstr* **16** 624-626, 1931.

but spectroscopic and quantitative chemical tests have failed to detect methemoglobin as the form of inactive oxyhemoglobin present in patients with thromboangitis obliterans

Sodium tetrathionate had a less immediate but more prolonged effect than did sodium thiosulfate. The more rapid oxidation and excretion of the thiosulfate as free sulfate in the urine may account for this difference.

CONCLUSIONS

Intravenous injections of sodium tetrathionate and sodium thiosulfate were usually followed by increased peripheral temperatures, decreased pulse rate and reduction in blood pressure. These physiologic responses were associated with changes in the oxygen capacity and in the oxygen saturation of the arterial and the venous blood.

These effects were opposite to those that occurred with smoking which is an important etiologic factor in thromboangitis obliterans. The therapeutic value of sodium thiosulfate and sodium tetrathionate is probably due to the changes produced in the blood and the resulting physiologic responses.

THERAPY OF PHLEBOTHROMBOSIS AND THROMBOPHLEBITIS

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Few conditions are as discouraging to the clinician and as unpleasant and dangerous to the patient as postoperative or postpuerperal thrombosis. There is nothing more tragic in medicine than the occurrence of a fatal pulmonary embolism in a patient who has convalesced satisfactorily after an operation and is ready to be discharged. Although less dramatic than such an outcome, persistent thrombophlebitic sequelae, such as post phlebitic edema, varicosities and ulceration, frequently cause the patient to regret having survived the original infection. All these conditions are similar in that an intravascular venous occlusion occurs, but we believe, as has been perviously emphasized,¹ that it is necessary from prognostic and therapeutic points of view to differentiate between thrombophlebitis and phlebothrombosis. In the former the intravascular clotting is associated with and dependent on inflammation of the wall of the vein, whereas in the latter there is no associated inflammatory process and because of this with absence of fixation of the thrombus to the vessel wall there is great danger of embolism. It is not the purpose of this presentation to discuss the causes of these two types of intravascular clotting. The reader is referred to previous publications.¹

The treatment of intravascular venous thrombosis may be outlined as follows

A Prophylaxis

- 1 Hydration
- 2 Mobilization
- 3 Respiratory stimulation
- 4 Prevention of increased abdominal tension
- 5 Application of heat (heat tent)
- 6 Administration of sodium thiosulfate
- 7 Hirudinization (leeches)
- 8 Heparinization

From the Department of Surgery, School of Medicine, Tulane University

1 Ochsner, A, and DeBakey, M. Thrombophlebitis and Phlebothrombosis, South Surgeon 8 269, 1939

B Conservative therapy

- 1 Immobilization and elevation
- 2 Application of heat
- 3 Hirudinization
- 4 Application of compression bandages
- 5 Vasodilatation
 - a Administration of parasympathetic stimulants
 - b Block of the sympathetic nerves with procaine hydrochloride

C Radical therapy

- 1 Ligation
- 2 Excision
- 3 Incision and drainage
- 4 Thrombectomy and embolectomy

Institution of prophylactic measures merely signifies avoidance of those factors which may be considered as precipitating the thrombotic process. Dehydration, which may occur postoperatively and which increases the viscosity of the blood, favors thrombosis and should be combated by adequate hydration of the patient. Coller and his associates² have demonstrated the frequency and the degrees of postoperative dehydration. That increased viscosity of the blood may occur postoperatively has been demonstrated by Zarubin³ and by Bolognesi.⁴ Similar observations were made by Lohr and Lohr,⁵ who also found that the viscosity paralleled the erythrocytic sedimentation rate. According to numerous observers,⁶ increase in the globulin fraction of the

2 Coller, F. A. Studies in Water Balance, Dehydration and Administration of Parenteral Fluids, *Minnesota Med* **19** 490, 1936. Coller, F. A., Dicks, V. S., and Maddock, W. G. Maintenance of Normal Water Exchange with Intravenous Fluids, *J. A. M. A.* **107** 1522 (Nov. 17) 1936.

3 Zarubin, cited by Matas, R. On the So-Called Primary Thrombosis of the Axillary Vein Caused by Strain. Report of a Case with Comments on Diagnosis, Pathogeny and Treatment of the Lesion in Its Medico-Legal Relations, *Am. J. Surg.* **24** 642, 1934.

4 Bolognesi, G. Untersuchungen über die Änderungen in der Blutviskosität infolge von chirurgischen Operationen. *Zentralbl. f. Chir.* **36** 1161, 1909.

5 Lohr, W., and Lohr, H. Ueber die Veränderung der physikalisch-chemischen Struktur der Blutflüssigkeit bei beschleunigter Blutkörperchen-senkung im Gefolge von Reizkörpertherapie, chirurgischen Operationen und Erkrankungen, *Ztschr. f. d. ges. exper. Med.* **29** 139, 1922.

6 (a) Rohrer, F. Bestimmung des Mischungsverhältnisses von Albumin und Globulin in Blutserum, *Deutsches Arch. f. klin. Med.* **121** 221 1917. (b) Naegeli, O. Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer 1919. (c) Heyder, cited by Naegeli. (d) Linzenmeier, G. Eine neue Schwangerschaftsreaktion und ihre theoretische Erklärung, *Arch. f. Gynäk.* **30** 608 1920. (e) Fåhræus, R. The Suspension-Stability of the Blood, *Acta med. Scandinav.* **55** 1 1921. (f) Lohr and Lohr.⁵

plasma augments the viscosity. The mechanism by which increased viscosity of the plasma per se aids in production of a thrombus is probably by favoring circulatory retardation. Thus, postoperative hydration becomes an important factor in the prevention of venous thrombosis.

The importance of circulatory retardation as a cause of intravascular clotting has been repeatedly emphasized. Circulatory retardation may be due to a number of causes. Among the various factors responsible is immobility. Other factors are anatomic peculiarities, posture hypopnea and increased abdominal tension. Any condition which will interfere with normal circulation in the vascular system may act as a precipitating factor and in the presence of predisposing factors may cause thrombosis. This has been emphasized particularly by Beneke⁷ and by Aschoff⁸. An anatomic factor, i. e., the peculiar relation of the left iliac vein to the right iliac artery, causing compression of the former, is uncontrollable. The other factors, however, are controllable and can be obviated. Posture may predispose to circulatory retardation. The placing of a patient in Fowler's position, with flexion of the thighs on the abdomen and flexion of the legs on the thighs at the knees, can result in compression of the vessels beneath the inguinal ligament and those in the popliteal space, respectively. Dependency of the lower extremity with the patient in the head-up (Fowler) position also predisposes to venous stasis. Cardiovascular activity is diminished postoperatively by the quiescence of the patient after an operative procedure. As the result of quiet rest in bed, the muscles of the extremities are relaxed, and return of venous blood to the heart is less rapid than normal. Circulatory activity is further decreased by peripheral vasoconstriction, this has been emphasized by Leriche⁹ and by Kvale¹⁰. Because of vasoconstriction in the capillary bed, venostasis occurs, which in turn predisposes to thrombosis. For these reasons, early postoperative mobilization in cases of venous thrombosis is essential as a prophylactic measure. Ries,¹¹

7 Beneke, R. Die Thrombose, in von Jagic, N. Handbuch der allgemeinen Pathologie, Diagnostik und Therapie der Herz- und Gefasskrankungen, Leipzig, Franz Deuticke, 1913, vol. 2, pt. 2, pp. 130-299.

8 Aschoff, L. Thrombosis, in Lectures on Pathology, New York, Paul B. Hoeber, 1924.

9 Leriche, R. Des moyens de reduire au minimum la maladie post-operative. De l'operatoire sous rayons infra-rouges, *Rev. de chir.* **74** 99, 1936.

10 Kvale, cited by Ward, C. E., and Horton, B. T. Postoperative Thrombophlebitis of the Inferior Vena Cava in a Child, *Proc. Staff Meet., Mayo Clin.* **12** 811, 1937.

11 Ries, E. Some Radical Changes in the After Treatment of Celiotomy Cases, *J. A. M. A.* **33** 454 (Aug. 19) 1899.

Richardson,¹² Boldt¹³ and others¹⁴ were early advocates of movement of the legs while the patient is in bed. More recently, the significance of such exercise has been emphasized again.¹⁵ Patients should be instructed to move their extremities frequently—as Wangenstein¹⁶ has suggested, at least a thousand times a day. Gamble¹⁷ has devised a bed bicycle for this purpose. Patey¹⁸ advocated placing the patient in the head-up position with a board under the feet to produce increased muscular tension.

Normal negative pressure within the thorax favors return of venous blood to the cardiac chambers. Because of the diminished respiratory activity which follows operation, there is interference with the normal venous return. Moreover, hypopnea occurs postoperatively as the result of pain caused by movement of the abdominal muscles and increase in abdominal tension. It has been shown repeatedly that postoperatively the diaphragmatic excursions are diminished, which results in concomitant increase in the intrapleural pressure, venous stasis and circulatory

12 Richardson, M. H. On Certain Unavoidable Calamities Following Surgical Operations, Boston M. & S. J. **151** 583, 1904.

13 Boldt, H. J. The Management of Laparotomy Patients and Their Modified After Treatment, New York M. J. **85** 145, 1907.

14 (a) Henle, cited by Pool^{14e} (b) Krecke, A. Ueber Vor- und Nachbehandlung bei Bauchoperationen insbesondere über das frühzeitige Aufstehenlassen, München med. Wchnschr. **57** 2037, 1910. (c) Wilson, L. B. Fatal Post-Operative Embolism, Ann. Surg. **56** 809, 1912. (d) Kleinschmidt, O. Die Nachbehandlung Laparotomierter, Ergebn. d. Chir. u. Orthop. **5** 432, 1913. (e) Pool, E. H. Systematic Exercises in Postoperative Treatment, J. A. M. A. **60** 1202 (April 19) 1913. (f) Vietor, J. A. Clinical Consideration of Thrombosis and Embolism, Ann. Surg. **82** 193, 1925.

15 (a) Schmid, H. H. Verhütung von postoperativen Thrombosen und Embolien, Zentralbl. f. Gynäk. **61** 307, 1937. (b) Voegt, H. Veränderungen der Wadenmuskulatur bei Venenthrombose und langem Krankenlager, Virchows Arch. f. path. Anat. **300** 190, 1937. (c) Knott, W. Ueber die Verhütung von postoperativen Thrombosen und Embolien durch die Hochlagerung nach H. H. Schmid, Zentralbl. f. Gynäk. **62** 679, 1938. (d) Shaw, W. F., and Rickard, C. E. B. Postoperative Exercises as Preventive of Embolism. J. Obst. & Gynec. Brit. Emp. **45** 451, 1938.

16 Wangenstein, O. The Therapeutic Problem in Bowel Obstruction, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

17 Gamble, H. A. The Prevention of Postoperative Embolism and Phlebitis, Am. J. Surg. **28** 93, 1935.

18 Patey, D. H. Artificially Induced Thrombophlebitis, Surg., Gynec. & Obst. **64** 1002, 1937.

retardation¹⁹ Prevention of hypopnea is therefore important, and patients should be instructed to take deep breaths frequently during their waking hours It is the custom in our clinic to have a patient take at least ten deep breaths every hour If the patient will not do this voluntarily, it can be accomplished by the use of carbon dioxide inhalations²⁰ Increased intra-abdominal pressure also favors circulatory retardation by exerting pressure on the intra-abdominal veins, interfering with the return flow of venous blood from the lower extremity Increased intra-abdominal tension may result from a number of factors, such as application of constricting bandages, which are frequently used by surgeons in an attempt to give support to the abdominal wall, and functional inactivity of the gastrointestinal tract, with its associated accumulation of fluid and gas in the intestine and stomach (ileus) For this reason, the increased intra-abdominal tension resulting from tight bandages or from ileus should be combated by avoidance of tight dressings, by use of appropriate devices, such as the indwelling catheter and by other methods previously described²¹ As was shown by Patey,^{19f} there is definitely increased intra-abdominal tension after an operation, apparently due to the decreased action of the diaphragm and splinting of the abdominal wall (presumably because of pain occasioned by movement)

Application of heat in the form of a heat tent to the lower part of the abdomen is undoubtedly of value after an operation, not only because of its beneficial effect on the tone of the intestine but probably because it produces vasodilatation of the peripheral vessels The extremely low incidence of intravascular clotting in our clinic is due, we believe, to the fact that heat tents are routinely applied to the abdomen postoperatively As these tents are large and cover the entire lower portion of the body applying as much heat on the lower extremities as on the abdomen, we

19 (a) Pasteur, W Massive Collapse of the Lung, *Lancet* **2** 1351, 1908 (b) Churchill, E D, and McNeil, D The Reduction in Vital Capacity Following Operations, *Surg, Gynec & Obst* **44** 483, 1927 (c) The Reduction in Vital Capacity, *Boston M & S J* **197** 83, 1927 (d) Muller, G P, Overholt, R H, and Pendergrass, E P Postoperative Pulmonary Hypoventilation, *Arch Surg* **19** 1322 (Dec, pt 2) 1929 (e) Brunn, H Atelectasis A Review of Its History, Significance and Treatment, *West J Surg* **38** 647, 1930 (f) Patey, D H The Effect of Abdominal Operations on the Mechanism of Respiration, with Special Reference to Pulmonary Embolism and Massive Collapse of the Lungs, *Brit J Surg* **17** 487, 1930 (g) Carlson, H A Inhibition of Respiration as a Factor in the Pathogenesis of Postoperative Pulmonary Complications, *J Thoracic Surg* **2** 196, 1932 (h) Prinzmetal, M, Brill, S, and Leake, C D Postoperative Pulmonary Subventilation, *Surg, Gynec & Obst* **56** 129, 1933

20 von Seeman, H Operation und Gewebeschonung II Beziehungen zwischen Operationswunde und Entstehung, Vermeidung und Bekämpfung der mittelbaren Operationschädigungen (spontane Venenthrombose und Pneumonie), *Deutsche Ztschr f Chir* **223** 85, 1930 Gamble¹⁷ Knott^{15c}

21 Ochsner, A Postoperative Treatment, *South M J* **29** 53, 1936

feel that the associated vasodilatation aids in preventing circulatory retardation

The use of sodium thiosulfate postoperatively as suggested by Bancroft and his associates²² for prevention of thrombosis may also be of value. This author and his co-workers, working on the theory that since there are potential "bleeders" there are potential "clotters," have devised a test for the plasma clotting index and one for fibrinogen. The prothrombin test, designated as the test for the plasma clotting index, is indicative of clotting tendencies when infection is at a minimum, while the fibrinogen test may suggest infection and the likelihood of thrombophlebitis. If examination of blood taken either preoperatively or postoperatively shows a high plasma clotting index and a high fibrinogen content, 10 cc. of a 10 per cent solution of sodium thiosulfate is administered intravenously on three successive days, the series being repeated after an interval of one day if the bleeding factors remain high. These authors have reported a large series of cases in which this procedure was followed by no thromboembolic accident.

Hirudinization and heparinization are also prophylactic measures based on anticoagulant activity. The former has been emphasized by one of us (Ochsner) in collaboration with Mahorner²³ and more recently by Chalier²⁴ and Rouhier²⁵. Crafoord²⁶ and Murray and Best and their co-workers²⁷ have reported interesting experimental and clinical investigations on the use of heparin in prevention of thromboembolic phenomena. These investigators found experimentally that by administering purified heparin intravenously over a period of hours it was possible to diminish the coagulation time considerably. They have applied the results of their investigations to human beings, and, although

22 (a) Bancroft, F. W., Stanley-Brown, M., and Quick, A. J. Postoperative Thrombosis and Embolism, *Am J Surg* **28** 648, 1935. (b) Bancroft, F. W., Stanley-Brown, M., and Chargaff, E. Postoperative Thrombosis and Embolism, *Ann Surg* **106** 868, 1937.

23 Ochsner, A., and Mahorner, H. The Use of Leeches in the Treatment of Phlebitis and the Prevention of Pulmonary Embolism, *Ann Surg* **98** 408, 1933.

24 Chalier, A. La prevention et le traitement abortif des phlebitis post-operatoires, *Presse med* **46** 1345, 1938.

25 Rouhier, G. A propos de l'utilisation des sangsues comme preventif des phlebitis post-operatoires, *Mem Acad de chir* **64** 356, 1938.

26 Crafoord, C. Preliminary Report on Postoperative Treatment with Heparin as a Preventive of Thrombosis, *Acta chir Scandinav* **79** 407, 1937; Heparin and Post-Operative Thrombosis, *ibid* **82** 319, 1939.

27 Murray, D. W. G., Jaques, L. B., Perrett, T. S., and Best, C. H. Heparin and Thrombosis of Veins Following Injury, *Surgery* **2** 163, 1937. Murray, D. W. G., and Best, C. H. Heparin and Thrombosis. Present Situation, *J A M A* **110** 118 (Jan 8) 1938. Best, C. H. Heparin and Thrombosis, *Brit M J* **2** 977, 1938.

an insufficient number of cases have been studied, the results have been satisfactory. Murray and Best have used a "saline and heparin mixture" which was allowed to run into the vein slowly, so that the clotting time of the patient's blood was maintained at about fifteen minutes. However, they stated that injection of heparin is now being restricted to cases in which extensive surgical procedures have been carried out and in which thrombosis is likely to occur.

CONSERVATIVE THERAPY

Immobilization and Elevation of the Extremity—This is a time honored method of treatment of thrombophlebitis. Its rational basis is the placing of the part at physiologic rest to minimize the danger of breaking off of an embolus and to relieve edema by favoring lymphatic flow. This form of therapy has a number of advocates.²⁸ A satisfactory method of immobilizing the entire extremity consists of applying a large sheet wadding dressing from the tips of the toes to the groin. Elevation of the extremity is accomplished either by elevation of the foot of the bed or by placing the involved extremity in a sling, on an inclined plane or on pillows. Heat may be applied in the form of a heat tent or by hot compresses. The purpose of application of external heat is to hasten the normal involution of the thrombus and periphlebitis, i. e., the inflammatory changes.

Hirudinization—Revival of the treatment of thrombophlebitis by leeches is credited primarily to Termier,²⁹ of France. In 1922 he³⁰ reported 19 cases, and three years later, 73 cases, of phlebitis treated by this form of therapy, with remarkable relief of acute manifestations. Subsequently, extensive reports appeared in the literature, especially in

28 (a) De Treigny, M. For How Long Must a Case of Phlebitis Be Immobilized? *Internat Clin* **10** 75, 1900. (b) Van der Veer, A. Phlebitis Following Abdominal Operations, *Tr Am Surg A* **19** 223, 1901. (c) Brothers, A. The Prophylaxis and Treatment of Postoperative Phlebitis, *Am J Obst* **55** 609, 1907. (d) Reisman, D. Phlebitis and Thrombosis, *M Clin North America* **4** 1005, 1921. (e) Bain, W. Phlebitis of the Lower Extremities and Superficial Veins of the Abdomen, *Lancet* **1** 701, 1927. (f) Brown, G. E. Postoperative Phlebitis. Clinical Study. *Arch Surg* **15** 245 (Aug.) 1927. (g) Rabinowitz, M. A., and Holtzman, I. N. Early Recognition of Peripheral Venous Thrombosis, *New York State J Med* **34** 973, 1934. (h) Homans, J. Venous Thrombosis in the Lower Limbs. Its Relation to Pulmonary Embolism, *Am J Surg* **38** 316, 1937. (i) McNealy, R. W. Treatment of Phlebitis, *S Clin North America* **17** 523, 1937.

29 Termier, J. Traitement abortif des phlébites chirurgicales avec lever precoce, *Proc-verb et mem Cong franç de chir* **31** 949, 1922.

30 Termier, J. Grenoble-Abortive Treatment of Surgical and Obstetrical Phlebitis Through Hirudinization (Application of Leeches), *Proc-verb et mem Cong franç de chir* **34** 434, 1925.

Europe, praising the brilliant results following this method of therapy³¹ Considerable experimental and clinical work with leeches has been done in the United States by one of us (Ochsner) with Mahoney³² The leech's salivary gland secretes hirudin, which can completely prevent the coagulation of blood and in vitro has been observed to cause dissolution of a blood clot Indeed Tenner concluded that the power of this substance to dissolve a blood clot explains the excellent effect obtained in

31 (a) Julliard Traitement de la thrombo-phlebite post-operative des membres inferieurs, Schweiz med Wchnschr **55** 515, 1925 (b) Gonnet, Jeannin, and Josserand De l'usage des sangsues dans les phlebitis puerperales, Lyon med **138** 657, 1926 (c) Beguer Thrombo-phlebite du membre inferieur Traite avec succes par les applications de sangsues, Arch med-chir de Province **17** 109, 1927 (d) Hamm, A., and Schwartz, A De l'emploi des sangsues dans le traitement des phlebitis, Schweiz med Wchnschr **57** 1125, 1927 (e) Monzon, J Le traitement des phlebitis thrombosantes par les sangsues, Presse med **35** 677, 1927 (f) Tholen, G A Die Behandlung post-operativen und puerperalen Thrombosen und Embolien, Wien klin Wchnschr **42** 1107, 1927 (g) ten Berge, B S Leeches in Venous Infections Case Nederl tijdschr v geneesk **1** 2893, 1928 (h) Chavannay, J., and Magnant, J À propos du traitement des phlebitis obliterantes par l'hirudinisation, Rev de chir **66** 461, 1928 (i) Ducuing, J Pourquoi le traitement des phlebitis chirurgicales par les sangsues semble-t'il donner de bons resultats? Progres med **43** 1787, 1928 (j) Ichok, G El empleo de las sanguijuelas en el tratamiento de las flebitis, Arch de med, cir y especialid **28** 747, 1928 (k) di Pace, I La irudinizzazione delle flebitis, Gazz d osp **49** 73, 1928 (l) Vidal Traitement par des applications de sangsues d'un cas de phlebite puerperale a debut embolique, Bull Soc d'obst et de gynec **17** 36, 1928 (m) Coggi, C A proposito dell irudinizzazione delle thromboflebitis in ostetricia e ginecologia, Ann di ostet **51** 1457, 1929 (n) Muresanu, B Clinical Considerations on the Treatment of Post-Operative Phlebitis with Leeches, Rev de chir, Bucuresti **21** 592, 1929 (o) Sulger, E., and Boszin, T Ueber die post-operative Thrombose und Embolie sowie ihre therapeutische und prophylaktische Behandlung mit Blutegeln, Deutsche Ztschr f Chir **216** 175, 1929 (p) Mayer, L À propos de l'embolie post-operative, Bruxelles med **10** 312, 1930 (q) Angelì, A La irudinizzazione nelle flebitis, Rassegna internaz di clin e terap **12** 1180, 1931 (r) Chaliè, A Sur la prophylaxie des phlebitis et embolies postoperatoires en gynecologie, Bull et mem Soc nat de chir **57** 216, 1931 (s) Dimitriu, V., and Somnea, G O Action therapeutique de l'hirudine dans les phlebitis, la septicemie et dans quelques affections de nature microbienne, Presse med **39** 1359, 1931 (t) Rossi, G La irudinizzazione nelle flebitis postoperatorie e puerperali, Policlinico (sez prat) **38** 989, 1931 (u) Oden, H G Zur Blutegeltherapie der Thrombo-phlebitis, Med Welt **7** 273, 1933 (v) Straaten, T Die Blutegeltherapie der Thrombose, Deutsche Ztschr f Chir **238** 513, 1933 (w) de Donno, E Sulla terapia delle thromboflebitis puerperali e postoperatorie con la fasciatura con cerotto, Clin ostet **36** 647, 1934 (x) Haupt, W Zur Thrombosenbehandlung und—Verhütung mittels Blutegel, Verhandl d deutsch Gesellsch f Kreislaufforsch, 1934, p 189 (y) Hauptstein, P Die Blutegelbehandlung der Thrombophlebitis (Thrombose) nach Operationen und im Wochenbett, Med Welt **8** 1723, 1934 (z) Hempel, C Die medizinische Anwendung des Blutegels im Wandel der Zeiten

cases of thrombophlebitis. Others have suggested as an explanation for the good results observed from this form of therapy an increase in phagocytic and bactericidal powers,³³ local blood letting,³¹⁰ prevention of venous spasm^{31d} and general humidization³⁴

The efficacy of this form of therapy in cases of phlebitis has been reported by numerous investigators. In 1933, one of us (Ochsner) in collaboration with Mahorney²³ reported 3 cases of phlebitis and 1 of thromboangitis obliterans in which it was used and was followed by rapid abatement of symptoms. Recently, Lilienthal,³⁵ Magnus³⁶ and Pardella³⁷ have also reported good results. Chalier²⁴ and Rouhier²⁵ have recently reported its use as a preventive measure. Rouhier²⁵ stated, however, that once thrombophlebitis occurs the leeches should not be applied, because of the possibility of development of an embolism. Moulouguet³⁸ and Ameline³⁹ also stated that they have given up the use of leeches for phlebitis because of the occurrence of emboli after their application. We have never observed any bad results from the use of leeches, however, and we still believe that there are many conditions, such as portal thrombophlebitis (pylephlebitis), in which humidization is one of the most valuable methods of therapy, if not the most valuable.

Heparinization—Heparin has been used in the treatment of thrombophlebitis. Murray and Best and their associates²⁷ reported 28 cases in which it was employed. They observed no evidence of embolism in any of these. The clinical signs and symptoms, pain, swelling, tenderness and fever, appeared to show more rapid improvement than was observed in a control group.

mit neueren Daten aus Zoologie, Physiologie und Pharmakologie, *ibid* 8 210, 1934 (a¹) Macciotta, M. L'irudinizzazione nelle flebiti e nelle forme infiammatorie ginecologiche, *Clin ostet* 36 36, 1934 (b¹) Pascalis, G. Chirurgie pelvienne et phlebitis, *Rev gen de clin et de therap* 48 279, 1934 (c¹) Bolli, E. V. Il metodo Termier nella cura delle flebiti puerperali e postoperatorie. Rassegna bibliografica e contributo personale, *Arch di ostet e ginec* 42 475, 1935 (d¹) Meyer, E. Die Blutegelbehandlung von Thrombosen und Thrombophlebitiden, *Therap d Gegenw* 76 18, 1935 (e¹) Leuze, A. M. Technik der Blutegelbehandlung, *Munchen med Wchnschr* 83 315, 1936 (f¹) Rudiger. Zur Blutegelbehandlung, *ibid* 83 1276, 1936 (g¹) Wimhofer, H. Die Bedeutung der Blutegelbehandlung in der Therapie und Prophylaxe der postoperativen Thrombose, *Ztschr f Geburtsh u Gynäk* 117 397, 1938

32 Ochsner, A., and Mahorney, H. Bactericidal Effect of Hirudin and Heparin. I. Intravenous Injection of Hirudin and Heparin and Leeching in Experimental Bacteremia, *Arch Surg* 31 308 (Aug.) 1935. Mahorney, H., and Ochsner, A. Bactericidal Effect of Hirudin and Heparin. II. Growth of Organisms in Blood Rendered Incoagulable with Hirudin and Heparin, *ibid* 31 371 (Sept.) 1935. Footnote 23

Compression Bandages—Application of compression devices, such as elastic adhesive plaster or Unna's paste boot, has also been advocated for treatment of thrombophlebitis. Fischer⁴⁰ is usually credited with being the first to advocate this form of therapy for the early stages of the disease, although Rupp⁴¹ had previously advocated it as a prophylactic measure. This method of therapy has recently received considerable approbation by Friedlander,⁴² Muller,⁴³ Stotzer⁴⁴ and Pratsicas and Theohari.⁴⁵

Vasodilatation—The use of vasodilatory measures in the treatment of thrombophlebitis has recently received considerable attention. Murphy⁴⁶ and, more recently, Sokolov and Meyers⁴⁷ have advocated iontophoresis with acetylbetamethylcholine hydrochloride (mecholyl). Murphy reported favorable results with this form of therapy in 33 cases of thrombophlebitis. Nineteen patients with thrombophlebitis of the deep veins were treated by this method by Sokolov and Meyers, and improvement was noted in 18. However, only 3 of these were in the acute stages, although the authors stated that the best improvement was obtained in the cases of acute involvement. Vasodilation by means of artificially induced fever has been suggested by Eveymeersch and Snoeck⁴⁸ and by Pitfield.⁴⁹ The former authors used injections of sterile milk to produce the fever, and the latter author used injection of typhoid vaccine. Irradiation therapy has also been suggested, by Halban⁵⁰ and by Henschen and Becker.⁵¹ Paine and Levitt⁵² have recently reported the use of intermittent venous occlusion in the treatment of thrombophlebitis. This method of therapy was employed in 4 cases of acute thrombophlebitis and in 7 of the chronic form, with relief of pain, tenderness and discomfort. Edema was decreased in some cases and unaffected in others.

33 Bosc, F. J., and Delezenne. De l'immunité conférée par quelques substances anticoagulantes, de son mécanisme, excitation de la phagocytose, augmentation du pouvoir bactéricide du sang, *Compt rend Acad d sc* **123** 500, 1896

34 Henschen, cited by Sulger and Boszin.³¹⁰

35 Lihenthal, H., in discussion on Bancroft, Stanley-Brown and Chargaff.^{22b}

36 Magnus, G. Blutegelbehandlung bei Thrombosebereitschaft, *München med Wchnschr* **84** 1992, 1937

37 Pardella, C. Sulla cura delle thrombose e delle thromboflebiti degli arti, *Ann di ostet e ginec* **60** 973, 1938

38 Moulounguet, in discussion on Rouhier.²⁵

39 Ameline, in discussion on Rouhier.²⁵

40 Fischer, cited by Friedlander.⁴²

41 Rupp. Zur Verhütung postoperativer Thrombophlebitis, *Zentralbl f Chir* **58** 1444, 1931

42 Friedlander, E. Die Kompressionsbehandlung der Venenentzündung. *Wien klin Wchnschr* **48** 791, 1935

In our experience, the best method of therapy and the one which has given by far the best results is production of vasodilatation passively by blocking with procaine hydrochloride the regional sympathetic ganglions, as suggested by Leriche⁵³ In 1934, Leriche and Kunlin⁵⁴ reported 3 cases of acute postoperative phlebitis successfully treated by procaine hydrochloride block of the lumbar sympathetic ganglions Since then Kunlin, Leriche and others⁵⁵ have reported other cases in which similar results were obtained Numerous other reports⁵⁶ attest the success of this method of therapy According to Leriche and Kunlin,⁵⁷ the mechanism of development of clinical manifestations of

43 Muller, A Die Thrombophlebitis und ihre Behandlung mit komprimerendem Gehverband, *Med Klin* **33** 793, 1937

44 Stotzel, E Zur Phlebitis und deren ambulanten Behandlung, *Schweiz med Wchnschr* **67** 476, 1937

45 Pratsicas, A, and Theohari, C La traitement de la phlebite aigue des membres inferieurs par la compression precoce, *J de med de Lyon* **19** 367, 1938

46 Murphy, H L Treatment of Thrombophlebitis with Acetyl-Beta-Methyl Choline Chloride Iontophoresis, *Surg, Gynec & Obst* **65** 100, 1937

47 Sokolov, R A, and Meyers, M P The Treatment of Deep Thrombophlebitis and Chronic Leg Ulcers with Acetyl-Beta-Methyl Choline Chloride Iontophoresis, *Am Heart J* **17** 316, 1939

48 Eveymeersch, A, and Snoeck, J Essai de protomotherapie non-specifique dans les phlebites aigues du post-partum (injections de lait), *Bruxelles med* **15** 98, 1934

49 Pitfield, R L Induction of Therapeutic Crises by Typhoid Vaccine in Septic Phlebitis, *M Rec* **145** 147, 1937

50 Halban, cited by McNealy²⁸¹

51 Henschen, C, and Becker, F Rontgenbestrahlung der akuten, der subakuten und der chronischen Phlebitis und Thrombophlebitis, *Schweiz med Wchnschr* **67** 438, 1937

52 Paine, J R, and Levitt, G The Treatment of Thrombophlebitis of the Deep Veins of the Lower Extremities with Intermittent Venous Occlusion, *Surgery* **5** 707, 1939

53 (a) Leriche, R Traitement chirurgical des suites eloignees des phlebites et des grands oedemes non medicaux des membres inferieurs, *Bull et mem Soc nat de chir* **53** 187, 1927, (b) Sur l'importance de la periphlebite dans la genese des accidents tardifs, consecutifs aux obliterations veineuses, *ibid* **53** 561, 1927 (c) Leriche, R, and Kunlin, J Traitement immediat des phlebites post-operatoires par l'infiltration novocaïnique du sympathique lombaire, *Presse med* **42** 1481, 1934

54 Leriche, R, and Kunlin, J Tratamiento inmediato de las flebitis post operatorias por la infiltracion novocaïnica del simpatico lumbar, *Cron med mex* **33** 389, 1934, footnote 53 c

55 (a) Kunlin, J, and Lucinesco, E Resultats du traitement immediat des phlebites post-operatoires et variqueuses par l'infiltration novocaïnique du sympathique lombaire Cinq nouvelles observations, *Bull et mem Soc nat de chir* **61** 965, 1935 (b) Houot, A Infiltrations stellaires dans une thrombophlebite du membre superieur par effort, *Progres med*, 1937, p 492 (c) Leriche, R Considerations sur le traitement chirurgical de la phlebite du membre inferieur et de ses sequelles eloignees, *J internat de chir* **3** 585, 1938

thrombophlebitis is the initiation of a vasomotor reflex as the result of impulses originating in the thrombosed venous segment (fig 1) Apparently, Leriche^{55c} is of the opinion that there are three prominent factors in this process, namely, venospasm, coagulation and arterial spasm. By block of the sympathetic ganglions with procaine hydrochloride this vasomotor reflex is broken, and the clinical manifestations are relieved (fig 2).

We⁵⁸ have shown by clinical and experimental observations that vasospasm resulting from impulses originating from involved venous segments is one of the most important factors in the production of the clinical manifestations of thrombophlebitis. Such vasospastic influences probably affect both arterioles and veins (figs 1 to 3). Numerous investigators⁵⁹ have shown that a localized thrombophlebitic process can initiate a marked vasospasm. Indeed, the vasospasm may be so

56 (a) Bourgalt, E. Traitement des phlebitis par anesthésies temporaires de la chaîne sympathique lombaire, *J de l'Hotel-Dieu de Montreal* **4** 212, 1935 (b) Aufrère and Mathieu. L'infiltration du sympathique lombaire dans le traitement immédiat des phlebitis post-opératoires, *Lyon med* **158** 169, 1936 (c) Dignonnet, Chenebault, and Rouchy. Deux cas de phlebite puerperale, traités par novocaïnisation du sympathique lombaire, *Bull Soc d'obst et de gynec* **25** 215, 1936 (d) de Souza Rudge, W. Tratamento immediato das phlebitis post-operatorias pela infiltração novocâmica do sympathico lombar, *Rev de gynec e d'obst* **30** 833, 1936 (e) de Oliveira Figueiredo, I. Tres casos de phlebitis puerperales tratados pelo methodo de Leriche, *ibid* **31** 199, 1937 (f) Massart, R. L'infiltration analgesique des ganglions sympathiques en particulier du ganglion étoile et du deuxième ganglion lombaire (étude d'une centaine de cas), *Bull et mem Soc de chir de Paris* **29** 91, 1937 (g) Caiero, J. A. La sección funcional del simpático por la novocaïnización del ganglio estelar y del simpático lumbar. Técnica de la inyección, *Dia med* **10** 779, 1938 (h) Fasano, M. La cura della flebite post-operatoria con il metodo di Leriche, *Boll e mem Soc piemontese de chir* **8** 61, 1938 (i) Gregoire, R. La repercussion de l'inflammation des veines sur le système arteriel collatéral, *Mem Acad de chir* **64** 363, 1938 (j) Demarez, R., and Linquette, M. Le traitement immédiat des phlebitis post-opératoires par l'anesthésie du sympathique lombaire, a propos de quatre observations personnelles, *Echo med du Nord* **10** 12, 1939

57 Leriche and Kunlin^{55c} Leriche and Kunlin⁵⁴ Leriche^{57c}

58 (a) DeBakey, M., Burch, G. E., and Ochsner, A. Effect of Chemical Irritation of Venous Segment on Peripheral Pulse Volume, *Proc Soc Exper Biol & Med* **41** 585, 1939 (b) Ochsner, A., and DeBakey, M. Thrombophlebitis. The Role of Vasospasm in the Production of the Clinical Manifestations, *J A M A* **114** 117 (Jan 13) 1940

59 (a) Pallin, G. The Differential Diagnosis. Arterial Embolism, Venous Thrombosis, *Acta chir Scandinav* **65** 558, 1929 (b) Tremolieres, F., and Veran, P. Syndrome d'obliteration arterielle du membre inferieur droit apparu au cours d'une phlebite superficielle et profonde avec embolies pulmonaires. Effet therapeutique de l'acetylcholine, *Bull med, Paris* **43** 1101, 1929 (c) Låwen, A. Arteriospasmus bei akuter massiver Thrombose der V femoralis, *Zentralbl f*

marked that the condition appears to be arterial embolism,⁶⁰ and in some instances actual gangrene⁶¹ has occurred. We have conducted experiments on animals which show convincingly that localized chemical endophlebitis may produce such marked arteriolar vasospasm that practically all pulsation disappears. Moreover, it is possible to demonstrate that this mechanism is the result of vasoconstrictor impulses originating in the involved segment and transmitted over the sympathetic nervous system (fig 3). In another publication⁵⁸ we have reviewed the mechanism by which vasospasm in thrombophlebitis can produce edema. Briefly, the factors which result from vasospasm and increase the amount of perivascular fluid are (1) increased filtration pressure, (2) anoxia of the capillary endothelium and (3) diminution in the flow of lymph. We have determined the venous pressure in 8 cases and found it to be four to five times that of normal (fig 3). This increase in venous pressure obviously increases the filtration pressure, which favors transudation of the fluid from the vascular into the perivascular spaces. Because of the associated arteriolar spasm and evidences of diminished vascularity, there probably occurs a relative anoxia of the capillary endothelium, favoring increased permeability of this membrane and consequent increased transudation of vascular fluid into the perivascular spaces. That edema is greatly influenced by the presence or absence of normal arteriolar pulsations has been demonstrated by the experiments of McMaster and Parsons⁶² and by those of Cressman and Blalock.⁶³

Chir **61** 1681, 1934 (d) Audier, M. La symptomatologie arterielle des phlébites des membres et de leurs séquelles, *Progres med*, 1935, p 729 (e) Nicole, R. Arteriospasmus bei akuter Venenthrombose, *Schweiz med Wchnschr* **65** 676, 1935 (f) Gardere, H, and Desjacques, R. Phlébite du membre inférieur simulant une embolie artérielle, diagnostic différentiel par l'acécoline, *Presse med* **45** 158, 1937 (g) Lawen, A. Ueber Thrombektomie bei Venenthrombose und Arteriospasmus, *Arch f klin Chir* **189** 53, 1937 (h) Lawen, A. Ueber Thrombektomie bei Venenthrombose und Arteriospasmus, *Zentralbl f Chir* **64** 961 1937, abstracted, *ibid* **64** 1239, 1937 (i) Lindgren, S. Arterienemptome bei den tiefen Bein thrombosen, *Upsala lakaref forh* **42** 415, 1937 (j) Audier, M. L'acetylcholine dans le traitement des phlébites des membres, *Monde med* **48** 17, 1938 (k) Chevrier, in discussion on Gregoire,⁶¹ p 367 (l) Cornil, L, and Audier, M. Les phlébarterites des membres, *J med franç* **27** 337, 1938 (m) Mondor, in discussion on Gregoire,⁶¹ p 367 (n) Pamparì, D. Tromboflebite acuta degli arti e fenomeni pseudo-embolici, *Pol clinico (sez chir)* **45** 470, 1938 (o) Pesnel, P. À propos de spasmes des vaisseaux des membres inférieurs consécutifs à des affections veineuses. *Semaine d hôp de Paris* **14** 378, 1938 (p) dos Santos, J C. La phlebographie directe, conception, technique, premiers résultats, *T internat de chir* **3** 625, 1938, (q) Spasme veineux du bras après injection intra-artérielle, action de l'infiltration du ganglion étoile, contrôle phlebographique avant et après l'infiltration, *Rev de chir* **76** 308, 1938 (r) Uggeri, C, and Massone, A. La sintomatologia arteriale delle flebiti degli arti, *Arch ital di chir* **49** 429, 1938

who showed that in the absence of pulsations there was almost no movement of lymph but that in the presence of pulsations the lymph flow was rapid. Monteiro⁶⁴ has shown also that blocking of the sympathetic nerves increases the flow of lymph. We⁵⁸ have shown experimentally and clinically that in the presence of a thrombophlebitic process the volume of peripheral arteriolar pulsation is considerably diminished and that in many instances the pulsation is almost imperceptible (fig 3). This is due not only to the associated vasospasm but to increased venous pressure.⁶ The decrease in lymph flow results in stagnation of tissue fluids and accumulation of proteins in the perivascular fluid, thus setting up a vicious circle in that the pressure of the perivascular fluid approaches that of the fluid within the vessel, tending to prevent resorption of fluid from the perivascular spaces into the vascular tree. Thus, it is evident that vasoconstrictor impulses originating in a thrombophlebitic process play a significant role in production of the clinical manifestations of thrombophlebitis. When the vasoconstrictor impulses are interrupted by infiltration of the sympathetic ganglions with procaine hydrochloride, there is produced a reestablishment of the normal exchange of intervascular and perivascular fluids and a breaking up of the vicious circle.

60 (a) Bergeret, A., Guillaume A. C., and DeLarue, J. Gangrene ischemique du membre inferieur par thrombose obliterante de la totalite des veines, *Ann anat path* **9** 536, 1932. (b) Wertheimer, P., and Friehe, P. Thromboses veineuses, obliterations arterielles et gangrene des membres, documents cliniques *Presse med* **43** 1004, 1935. (c) Audier, M. Thromboses veineuses aigues simulant l'embolie arterielle des membres, *Paris med* **1** 384, 1936. (d) Fontaine, R. Israel, L., and Pereira, S. A propos d'un cas de thrombose de la veine cave inferieure. Thrombo-phlebitis simulant les embolies arterielles et gangrenes d'origine veineuse, *J de chir* **47** 926, 1936. (e) Audier, M., and Haimovici, H. Les gangrenes des membres d'origine veineuse, *Presse med* **46** 1403, 1938. (f) Banzet, P., in discussion on Gregoire,⁵⁶¹ p 367. (g) Gregoire, R. La phlebite bleue (phlegmasia cerulæ dolens), *Presse med* **46** 1313, 1938. Pallin⁵⁹¹ Tremolieres and Veran^{59b} Lawen^{59c} Lindgren⁵⁹¹ Chevrier^{59k} Pampari⁵⁹ⁿ

61 Tilley, J. H. Gangrene of Extremities in Thrombophlebitis, *Am J Obst & Gynec* **36** 157, 1938. Decouls, P., and Bastien, P. Gangrene par spasme arteriel au cours d'une phlebite, *Ann anat path* **16** 353, 1939. Bergeret and his associates⁶⁰¹ Fontaine and his associates^{60d} Audier and Haimovici^{60e}

62 McMaster, P. D., and Parsons, R. J. The Effect of the Pulse on the Spread of Substances Through Tissues, *J Exper Med* **68** 377, 1938. Parsons R. J., and McMaster, P. D. The Effect of the Pulse upon the Formation and Flow of Lymph, *ibid* **68** 353, 1938.

63 Cressman, R. D., and Blalock, A. The Effect of the Pulse upon the Flow of Lymph, *Proc Soc Exper Biol & Med* **41** 140, 1939.

64 Monteiro, H. La lymphangiographie chez le vivant, Methode, resultats et application, *Bruxelles med* **19** 205, 1938, La lymphangiographie chez le vivant, methode, resultats et application *ibid* **19** 242, 1939.

65 Burch, G. E., DeBakey, M., and Sodeman, W. Effect of Venous Pressure on Pulse Volume, *Proc Soc Exper Biol & Med* to be published.

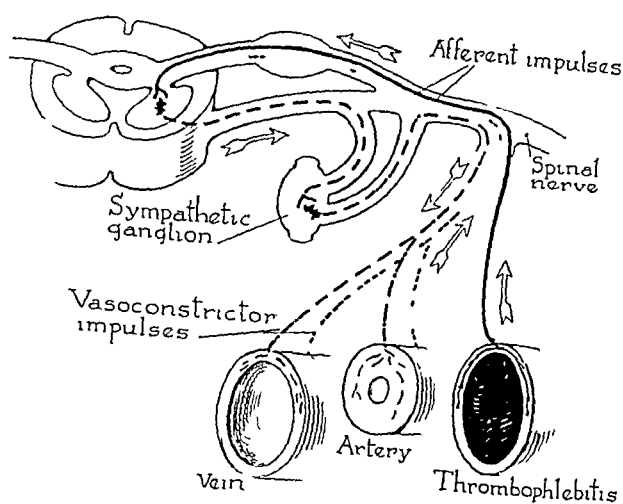


Fig 1—Diagrammatic representation of the mechanism of development of the clinical manifestations of thrombophlebitis. Impulses (depicted by arrow) originating in the thrombosed venous segment set up a vasomotor reflex resulting in generalized vasospasm of the involved extremity.

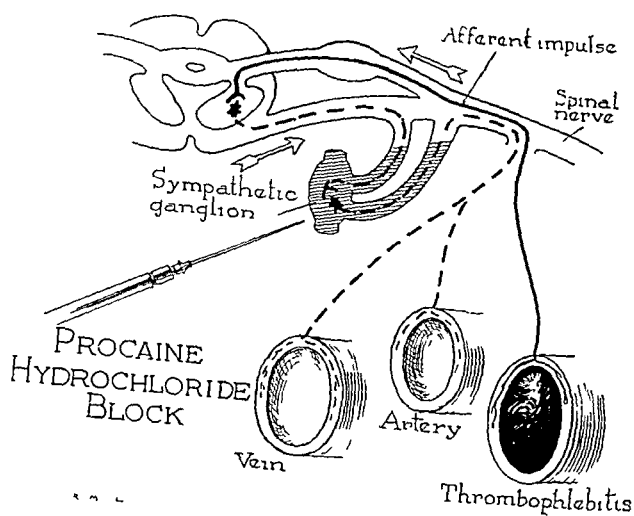


Fig 2—Diagrammatic representation of the mechanism of relief of the clinical manifestations after procaine hydrochloride block in cases of thrombophlebitis. Block of the sympathetic ganglions with procaine hydrochloride interrupts the vasoconstrictor impulses and results in breaking of the vasomotor reflex.

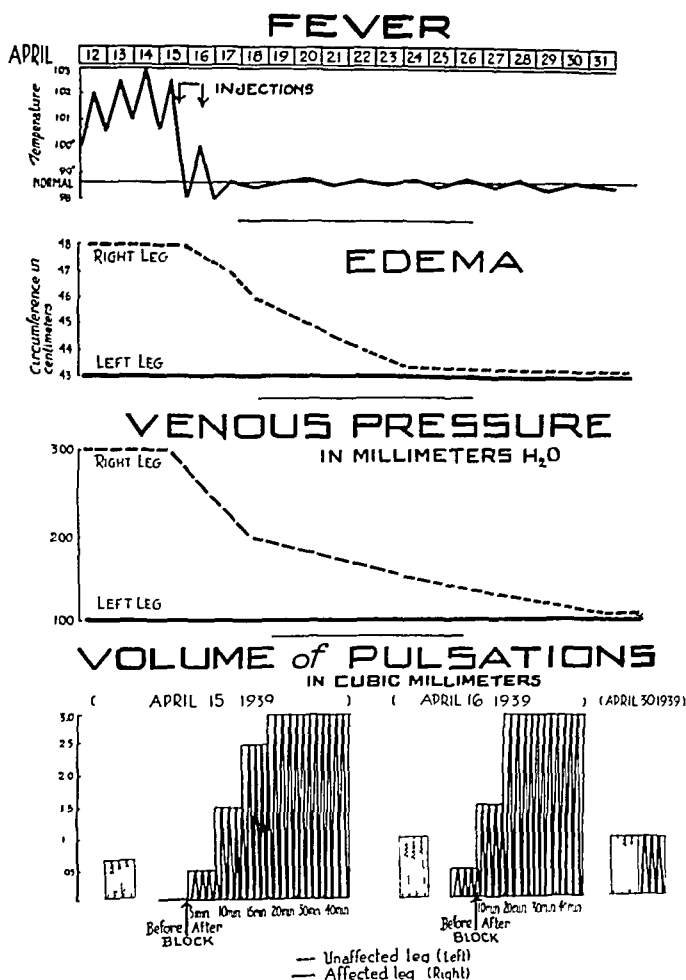


Fig 3—Graphic representation of the temperature, edema, venous pressure and volume of peripheral pulsations in a case of thrombophlebitis of the right lower extremity following cesarean section. The temperature ranged between 101 and 103 F but dropped to normal and remained there within forty-eight hours after the first "lumbar sympathetic block" (indicated by arrows). All swelling of the extremity had completely subsided seven days after therapy was begun. The venous pressure (taken in the saphenous vein at the ankle at heart level), which was 300 mm of water, rapidly dropped to less than 200 mm within three days of the first block and was practically normal within two weeks. The peripheral pulsations as determined plethysmographically were normal in the unaffected leg (left) but were practically absent in the affected leg (right) before block, suggesting vasospasm. Within ten minutes after block of the sympathetic fibers on the right, the pulsations were twice the volume of pulsations in the normal (left) leg, showing release of vasoconstrictor impulses. Similar observations, although less marked, were made the following day. On the day before the patient was discharged, peripheral pulsations in the right and in the left toes were equal.

We have reported elsewhere⁶⁶ the results of this form of therapy for thrombophlebitic processes. Since then, similar measures have been used in 5 additional cases, with prompt and permanent relief of all clinical manifestations. Pain has been relieved within fifteen minutes to a half an hour after the first injection in 86.3 per cent of the cases

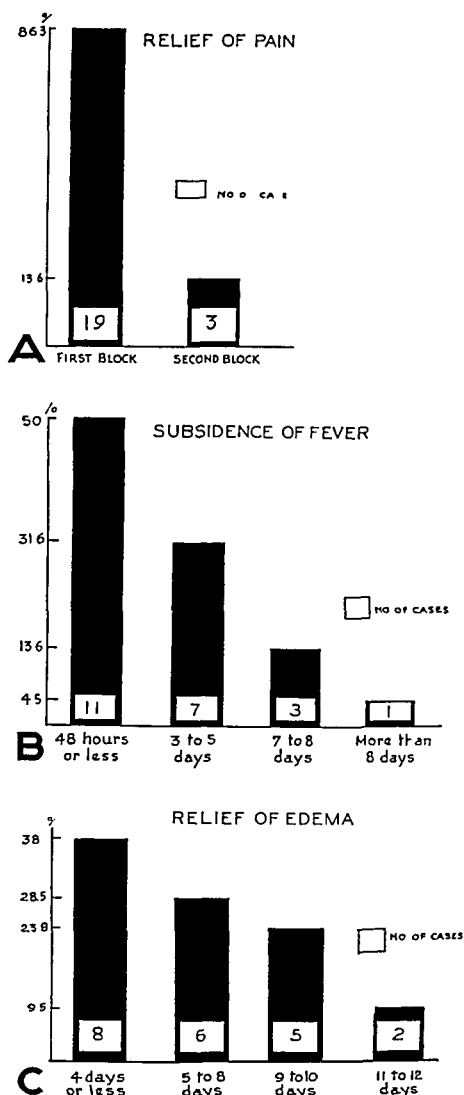


Fig 4—Graphic representation of (A) relief of pain, (B) subsidence of fever and (C) subsidence of edema after institution of "sympathetic block" with procaine hydrochloride in personally observed cases of thrombophlebitis

and in the remainder after the second injection (fig 4 A). Relief of pain was permanent. In no instance did the pain persist after the second

66 Ochsner, A, and DeBakey, M. Treatment of Thrombophlebitis by Novocaine Block of Sympathetics, *Surgery* 5: 491, 1939. Ochsner, A. Thrombophlebitis, *ibid* 6: 129, 1939. Ochsner and DeBakey.^{58b}

injection. Over half the patients were free from fever within forty-eight hours after institution of therapy (fig 4B). There were only 2 patients who had fever longer than one week, 1 for eight days and 1 for thirty-one days. The latter patient had a pulmonary infarct, although all of the thrombophlebitic manifestations of the extremity had completely subsided within nine days. This patient subsequently made a complete recovery. The subsidence of edema was unusually rapid. Eight patients showed complete subsidence of edema within four days. All but 2 of the patients had complete subsidence of edema within ten days, and in these 2 the edema had subsided on the eleventh and on the twelfth day respectively after institution of therapy (fig 4C). Two thirds of the patients were discharged from the hospital cured within eight days after institution of therapy and 90 per cent within twelve days (fig 5). Only 2 patients remained longer, 1 because of a pulmonary infarct and the other to permit more extensive experimental studies. Of particular interest are the follow-up observations on a number of these patients observed over periods varying from four months to over a year. In none has there been any evidence of recurrence of edema or of other postphlebitic manifestations. No other form of therapy was used in these cases.

We have used this method in 2 cases of "effort thrombosis." This interesting thrombotic phenomenon has been exhaustively reviewed by Matas⁶⁷. Others⁶⁸ have also described the severe clinical manifestations

67 Matas, R. On the So-Called Primary Thrombosis of the Axillary Vein Caused by Strain. Report of a Case with Comments on Diagnosis, Pathogeny and Treatment of the Lesion in Its Medico-Legal Relations, *Am J Surg* **24** 642, 1934.

68 Lowenstein, P. S. Thrombosis of the Axillary Vein. An Anatomic Study, *I A M A* **82** 854 (March 15) 1924. Schwindt, J. K. Traumatic Thrombosis of the Upper Extremity, *California & West Med* **27** 635, 1927. Gould, E. P., and Patey, D. H. Primary Thrombosis of the Axillary Veins. Study of Eight Cases, *Brit J Surg* **16** 208, 1928. Horton, B. T. Primary Thrombosis of the Axillary Vein, *J A M A* **96** 2194 (June 27) 1931. Paggi, B. Trombosi venose da sforzo degli arti superiori, *Polisclimico (sez. chir.)* **40** 383, 1933. Taylor, C. H. S. Primary Thrombosis of Subclavian Vein, *Brit M J* **2** 818, 1933. Piccagli, G. Trombosi da sforzo della vena ascellare destra, *Chir. d. org. di movimento* **19** 186, 1934. Ballou, H. C. Primary Thrombosis of the Axillary Vein, *Canad M A J* **32** 414, 1935. Barker, N. W. Axillary Thrombophlebitis Caused by Strain or Effort, *Proc. Staff Meet., Mayo Clin* **10** 156, 1935. Veal, J. R., and McFetridge, E. M. Primary Thrombosis of the Axillary Vein. An Anatomic and Roentgenologic Study of Certain Etiologic Factors and a Consideration of Venography as a Diagnostic Measure, *Arch Surg* **31** 271 (Aug.) 1935. Kaplan, T., and Katz, A. Thrombosis of Axillary Vein. Case Report with Comments on Etiology, Pathology and Diagnosis, *Am J Surg* **37** 326, 1937. Puhl, H.

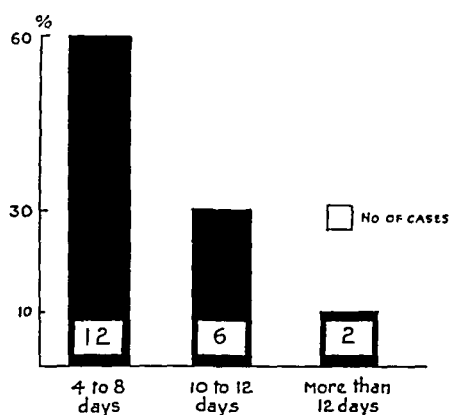


Fig 5—Graphic representation of the duration of hospitalization after institution of "sympathetic block" with procaine hydrochloride in personally observed cases of thrombophlebitis

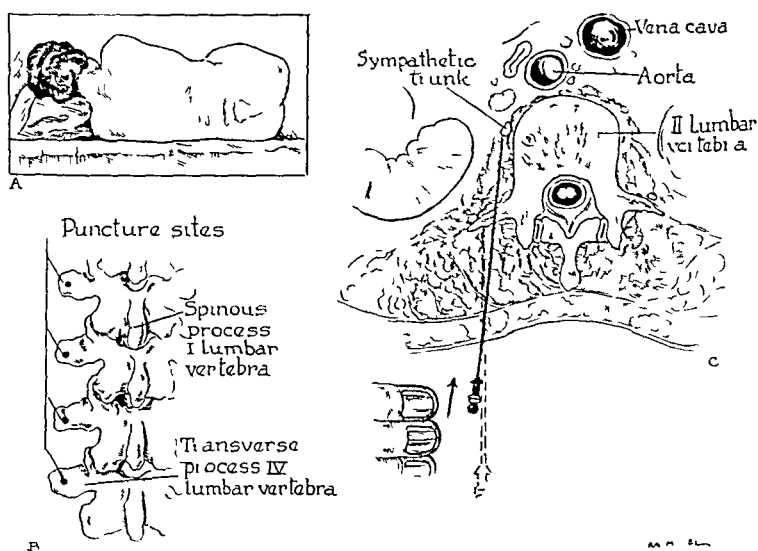


Fig 6—Diagrammatic illustration of the technic of "lumbar sympathetic block" for thrombophlebitis of the lower extremity *A*, patient in the lateral recumbent position *B*, cutaneous sites of puncture, lying immediately over the transverse processes of the vertebrae. They may be determined by taking points approximately $2\frac{1}{2}$ fingerbreadths lateral to and on a horizontal level with the spinous processes of the first four lumbar vertebrae *C*, insertion of the needles. Each needle is inserted vertically until the transverse process of the vertebra, as shown by the dotted needle, is reached. The direction of the needle is then changed slightly toward the midline, and the needle is inserted approximately $2\frac{1}{2}$ fingerbreadths beyond the transverse process, so that its point lies near the anterolateral surface of the body of the vertebra, where the sympathetic chain lies. Five cubic centimeters of 1 per cent procaine hydrochloride solution is injected through each needle, care being taken to determine previously that the needle is not in a vessel.

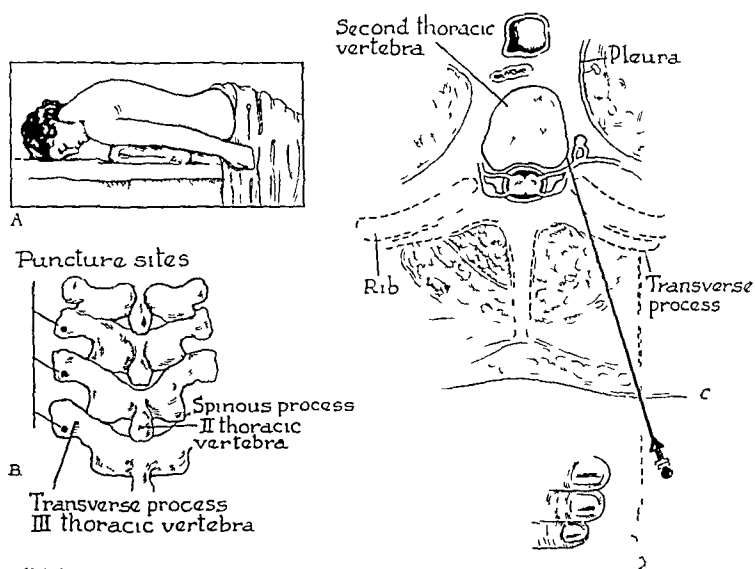


Fig 7—Diagrammatic illustration of the technic of cervicodorsal sympathectomy by the posterior approach *A*, patient in the prone position with pillows beneath the chest *B*, cutaneous sites of puncture, lying immediately over the transverse processes of the first, second and third thoracic vertebrae. They may be determined by taking points approximately $2\frac{1}{2}$ fingerbreadths lateral to and on a horizontal level with the spinous processes of the seventh cervical and the first and second thoracic vertebrae *C*, insertion of the needles. Each needle is inserted vertically until the transverse process, as shown by the dotted needle, is reached. The direction of the needle is then changed slightly toward the midline, and the needle is inserted $2\frac{1}{2}$ fingerbreadths beyond the transverse process, so that the point of the needle is near the anterolateral surface of the body of the vertebra in the retropleural space, where the sympathetic chain lies. Five cubic centimeters of 1 per cent procaine hydrochloride solution is injected through each needle.

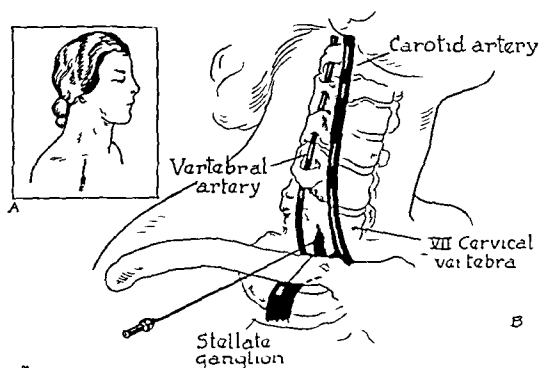


Fig 8—Diagrammatic illustration of the technic of block of the stellate ganglion by the anterior approach *A*, patient's head turned slightly toward the opposite side. The cutaneous site of puncture is approximately 1 cm medial to the midpoint of the clavicle and immediately over its upper border *B*, insertion of the needle posteriorly and medially at an angle of 45 degrees with the midline and on a horizontal level with the upper border of the clavicle.

which are so characteristic of the condition. Our 2 patients treated by sympathetic block were rapidly and permanently relieved.

The technic of injection of the anesthetic into the lumbar sympathetic ganglions is relatively simple and has been described previously.⁶⁶ The technic employed by us is illustrated in figures 6, 7 and 8.

RADICAL THERAPY

Although the conservative measures are generally adequate, resort to more radical procedures may occasionally become necessary. This applies particularly to the suppurative type of thrombophlebitis, in which ligation of the vein above the involved process may prevent further extension. Ligation of the vein proximal to a thrombophlebitic area was first performed by Hunter⁶⁹ in 1784. The procedure was also done by Lee⁷⁰ in 1865. Ligation or excision of the pelvic veins in the treatment of septic thrombophlebitis of puerperal origin has been advocated by Bumm,⁷¹ Sippel,⁷² Trendelenburg⁷³ and numerous

Zur Frage der sogenannten Thrombose der Vena axillaris, *Arch f klin Chir* **190** 569, 1937. Tomasi, L. Contributo alla patologia e alla clinica delle tromboflebiti dell'arte superiore, *Arch ital di chir* **43** 525, 1936, abstracted, *Internat Abstr Surg* **64** 171, 1937. Andersson, O. Venography in Case of So Called Traumatic Thrombosis of Axillary Vein, *Acta radiol* **19** 126, 1938. Kaplan, T. Thrombosis of Axillary Vein. Report of Five Cases with Comments on Etiology, Pathology and Diagnosis, *J A M A* **110** 2059 (June 18) 1938. Mason, J. M. Primary Thrombosis of Axillary Vein Caused by Strain, *Internat Clin* **1** 239, 1938. Wagner, W. Beobachtungen und Behandlung bei der sogenannten Achselvenenthrombose, *Zentralbl f Chir* **65** 2169, 1938. Zschau, H. Die sogenannte traumatische Thrombose der Vena axillaris und subclavia und ihre Begutachtung als Unfallfolge, *Munchen med Wchnschr* **85** 1990, 1938. Roelsen, E. So-Called Traumatic Thrombosis of Axillary and Subclavian Veins, *Acta med Scandinav* **98** 589, 1939.

69 Hunter, J. Observations on the Inflammation of the Internal Coats of Veins, *Tr Soc Improvement Med & Chir Knowledge* **1** 18, 1793.

70 Lee, H. The Surgical Treatment of Certain Cases of Acute Inflammation of the Veins, *M Times & Gaz* **1** 530, 1865.

71 Bumm, E. Ueber die chirurgische Behandlung des Kindbettfiebers, *Samml zwangl Abhandl a d Geb d Frauenh u Geburtsh* **4** 1, 1902. Zur operativen Behandlung der puerperalen Pyamie, *Klin Wchnschr* **44** 829, 1905. Operative Behandlung des Puerperalfiebers, *Zentralbl f Gynak* **33** 962, 1909. Ueber die operative Behandlung des Puerperalfiebers, *Verhandl d deutsch Gesellsch f Gynak* **13** 105, 1909.

72 Sippel, A. Die operative Behandlung der puerperalen Pyamie, *Zentralbl f Gynak* **26** 1361, 1902.

73 Trendelenburg, F. A Review of Surgical Progress, *J A M A* **47** 81 (July 14) 1906. Ueber die chirurgische Behandlung der puerperalen Pyamie, *Munchen med Wchnschr* **49** 513, 1902.

others⁷⁴ Briggs⁷⁵ advocated ligation of the saphenous vein in cases of recurrent phlebitis to prevent embolism, and Pool and McGowan⁷⁶ reported a case of femoral thrombophlebitis successfully treated by ligation of the femoral veins. Proximal ligation with or without excision has been suggested by numerous others⁷⁷. We have recently observed 1 case in which treatment by this means was successful. The patient was a white man 59 years of age who was admitted to the hospital complaining chiefly of pain and swelling in the left leg which began after an injury to the leg in an automobile accident. The traumatic thrombophlebitis of the popliteal vein responded readily to conservative therapy for approximately a week, after which the pain and swelling rapidly became worse, the patient had chills and the temperature rose to 104.8 F. The chills and hyperpyrexia recurred at six hour intervals, and the general condition of the patient appeared critical. Apparently a suppurative process had developed on the basis of the previous popliteal thrombosis, with production of recurrent septic emboli due to liquefaction

74 Lenhartz, H. Acht Fälle von operierter puerperaler septischer Thrombophlebitis, *Deutsche med Wchnschr* **32** 817, 1906. Seitz, L. Zur chirurgischen Behandlung der puerperalen Pyämie, *München med Wchnschr* **53** 2585, 1906. Williams, J. W. Ligation or Excision of Thrombosed Veins in the Treatment of Puerperal Pyaemia, *Am J Obst* **59** 758, 1909. Miller, C. J. The Present Status of Ligation or Excision of the Pelvic Veins in the Treatment of Septic Thrombophlebitis of Puerperal Origin, *J A M A* **59** 157 (July 20) 1912. Miller, C. J. Ligation or Excision of the Pelvic Veins in the Treatment of Puerperal Pyaemia, *Surg, Gynec & Obst* **25** 431, 1917. Rosenstein, P. Die Phlebektomie (operative Ausschaltung der fortschreitenden Thrombophlebitis), *Arch f klin Med* **109** 394, 1917. Kriele, J. Frühzeitige Diagnose und Prognose der Pyämie, *Ztschr f Geburtsh u Gynak* **99** 35, 1930.

75 Briggs, J. B. Recurring Phlebitis of Obscure Origin, *Bull Johns Hopkins Hosp* **16** 228, 1905.

76 Pool, E. H., and McGowan, F. J., Jr. Septic Thrombophlebitis of Femoral Vein. Operative Treatment, *Arch Surg* **8** 763 (May) 1924.

77 Lawen, A. Ueber die Rolle der Venen bei der Ausbreitung pyogener Prozesse, *Chirurg* **1** 682, 1929. Homans, J. Thrombophlebitis of the Lower Extremities, *Ann Surg* **87** 641, 1928. Dreyfuss, W. Die Phlebektomie als Behandlungsmethode der Thrombophlebitis und ihre Komplikationen, *Deutsche Ztschr f Chir* **217** 321, 1929. von Rehren, W. Ueber einen Fall von geheilter Extremitätenpyämie durch Unterbindung der Vena iliaca communis sinistra, *Zentralbl f Chir* **58** 1426, 1931. Stone, H. B. Surgical Treatment of Post-Operative Saphenous Thrombophlebitis, *Ann Surg* **96** 683, 1932. Neuhoof, H. The Diagnosis and Operative Control of Acute Pyogenic Phlebitis Complicated by General Septic Invasion, *ibid* **97** 808, 1933. Excision of Vein for Suppurative Thrombophlebitis, *ibid* **106** 311, 1937. Ranzi, E., and Huber, P. Postoperative Thrombose und Embolie, *Wien klin Wchnschr* **48** 289, 1935. Bancroft, F. W. Proximal Ligation and Excision of Veins for Septic Phlebitis, *Ann Surg* **106** 308, 1937. Sears, J. B. Embolism from Saphenous Thrombophlebitis and Its Prophylaxis, *New England J Med* **212** 874, 1935.

and breaking off of the infected clot. Approximately forty-eight hours after the onset of the septic manifestations the femoral and saphenous veins were exposed with the region under local procaine hydrochloride analgesia, and the saphenous vein was ligated just proximal to the saphenofemoral junction. After this, a block of the lumbar portion of the sympathetic nervous system was performed as has been described. Immediately after this, the pain and tenderness in the extremity were completely and permanently relieved. Within twelve hours the temperature returned to normal and remained normal (fig 9). The leg became warm, dry and pink, and in four days all swelling in it had subsided. The patient was discharged two days later.

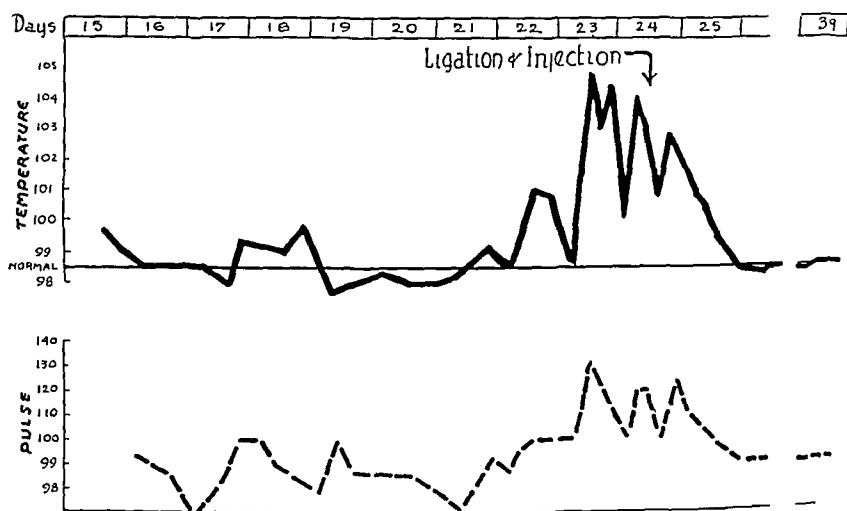


Fig 9—Graphic representation of the temperatures and pulse rates of a patient with septic thrombophlebitis. Ligation of the femoral vein and procaine hydrochloride block of the regional sympathetic nerves were performed.

Embolectomy (or thrombectomy) has also been suggested. Demons,⁷⁸ in 1881, reported its successful use in a case of suppurative thrombophlebitis of the median basilic and cephalic veins. Budinger⁷⁹ also advocated the procedure. Lawen⁸⁰ has repeatedly emphasized the significance of thrombectomy. It is his opinion that removal of the thrombus is of value not only because it prevents the occurrence of

78 Demons. Contributions au traitement antiseptique des phlébites, Bull et mem Soc de chir de Paris 7 878, 1881.

79 Budinger, K. Operativen Behandlung der akuten zirkumskripten Phlebitis, Wien klin Wchnschr 25 1217, 1912.

80 Lawen, A. Ueber Thrombektomie bei Venenthrombose und Arterio spasmus, Arch f klin Chir 189 53, 1937, Weitere Erfahrungen über operative Thrombenentfernung bei Venenthrombose, ibid 193 723, 1938, abstracted Zentralbl f Chir 65 1257, 1938.

emboli but because the presence of a thrombus in a venous segment acts as a focus for production of reflex vasospasm in that extremity. He has reported excellent results from this procedure. Kulenkampff⁸¹ has recently reported 61 cases and stated that after removal of the thrombus the saphenous vein should be ligated close to the femoral vein.

SUMMARY

The therapy of thrombophlebitis is reviewed and is classified into prophylactic, conservative and radical measures.

The prophylactic measures consist of hydration, mobilization, respiratory stimulation, prevention of increased abdominal tension, application of heat, administration of sodium thiosulfate, hirudinization and hepatinization.

The conservative measures consist of immobilization and elevation of the involved extremity, application of heat, hirudinization, use of compression bandages and production of vasodilatation.

In the authors' experience the best therapeutic measure is procaine hydrochloride block of the regional sympathetic nerves. The rationale of this therapeutic measure is discussed, and the excellent results obtained from its employment in 22 cases are described. The technic of "sympathetic block" as used by the authors is briefly described and illustrated.

The radical procedures consist of ligation, excision, incision and drainage and thrombectomy or embolectomy.

⁸¹ Kulenkampff, D. Die Verhütung schwerer oder tödlicher Embolien durch Ausraumung der Vena iliaca, *Arch f klin Chir* **193** 727, 1938, abstracted, *Zentralbl f Chir* **65** 1258, 1938.

LYMPHEDEMA OF THE LIMBS

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The states described here are those characterized by failure of the lymphatics to fulfil their function of draining the tissues of fluid which the blood capillaries are unable to accept. This failure may be due to an inherent defect in the lymphatic system, to an acquired organic blockage or to a disorder, once functional, which has become organic. Excluded from consideration are the nutritional edemas, the nephritic edemas, the cardiac edemas and the edemas of pregnancy, in short, all that are related to general or constitutional, as opposed to local, causes.

The tissue fluid is of course derived from blood. Such of it as is composed of water and salts reenters the blood capillaries, but plasma proteins and foreign material are unable to do so. Material of this sort and, in general, all substances whose contact with the body cells might harm the organism must, then, be carried off by the lymphatics. Just how such material, especially particulate matter, enters the lymphatics is not entirely clear and is not material here.

The ultimate lymph channels constitute a closed system, endothelium lined, which gathers itself into many tiny valved vessels capable of carrying lymph only toward the vena cava. These, following in the superficial tissues the general direction of the veins and in deeper parts circling about the great vessels, are gathered together at the root of the various limbs, where they pass, on their way to the thoracic duct, through great groups of lymph nodes. Exercise causes lymph to flow rapidly and abundantly, but in a flaccid limb it accumulates. Indeed, it behaves much like blood within the veins, it must be squeezed or pumped out of the limbs and in default of movement swelling occurs. Should venous pressure be raised, there is at first an increased flow of normal lymph but as the pressure is elevated more and more, the lymph changes in character, becoming highly proteinized and even containing red blood cells.

It must, then, be clear that lymphedema may result from many causes. Three principal groups are readily recognizable.

- 1 A group of edemas associated with disuse and injury and due primarily to failure of the lymphatics to dispose of tissue fluids normally produced.

2 A group of edemas associated with venous obstruction and due primarily to failure of the lymphatics to dispose of an excess of tissue fluids forced on them by elevated venous pressure

3 A group of edemas due to a natural or acquired deficiency of the lymphatics themselves, that is, elephantiasis

To these groups should be added several which are less well understood. Perhaps they are not lymphedemas in the ordinary sense, but

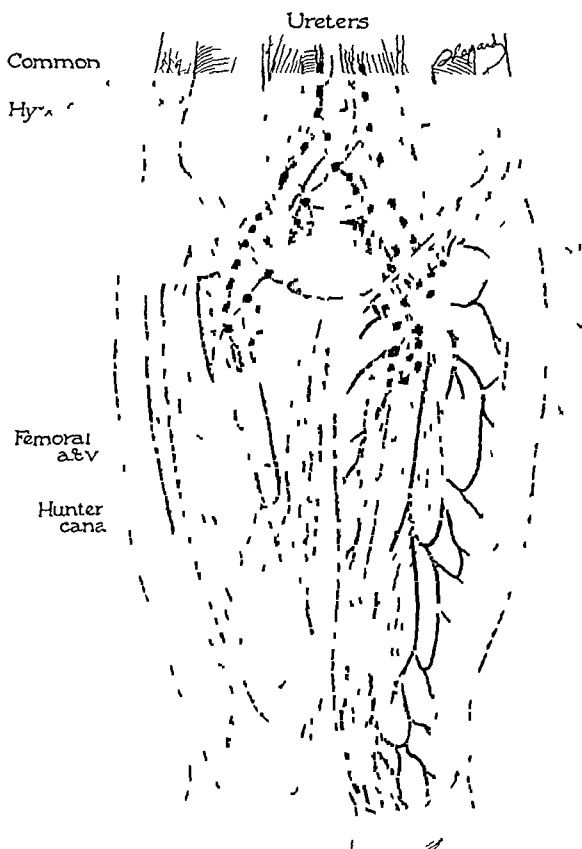


Fig 1—Lymphatics of the legs. In the left leg, some of the superficial lymphatics, which lie in the same plane with the superficial veins, are shown. These join the deep (perivascular) lymphatics at the groin. In the right leg, the deep lymphatics, which drain the back of the leg and foot, are represented. Rouviere's descriptions have in the main been followed.

they are confusable with them and must be identified and treated by special methods. Such are

4 A group of reflex or "trophic" edemas related to countless causes and including the causalgia-like states

5 A group of allergic edemas, due to hypersensitiveness to foreign substances, especially the fungi of the skin

6 Cavernous lymphangiomas

The lymphedemas, or, if one prefers, swellings, peculiar to the limbs will be considered here in the order just outlined and under the following headings (1) edemas directly due to disuse and injury, (2) edemas due to venous thromboses, (3) elephantiasis, (4) reflex edemas, (5) allergic edemas, and (6) cavernous lymphangiomas¹

EDEMAS DUE TO DISUSE AND INJURY

Since the borderline between swelling and no swelling in a limb is narrow, edema due to the muscular atrophy which results from confinement to bed is very common. After even a few weeks in bed, and all the more after many months, some persons notice swelling of the ankles on first getting about. Since it is the pumping mechanism which is deficient, the edema quickly disappears on elevation of the limb. It disappears overnight and returns during the day until such time as the muscles regain their tone and the patient his normal activity. This sort of edema should be kept in mind, because it may be confused with the onset of a late and quiet phlegmasia alba dolens, from which it is distinguished by its daily development and nightly disappearance and by the absence of any discomfort.

A similar edema is associated with the late effect of sprains and fractures, that is, those which leave stiff joints and atrophied muscles. It may even be noticed in some persons who have badly pronated feet which they use ineffectively, and it is common in aged persons, inactive who do much standing about.

In all such states the swelling disappears on a night's rest in bed. It is very different from the acute edema of a sprain, which is either an exudate or, as Leriche would have one believe, a result of a sympathetic dysfunction due to trauma (as such it will be discussed with the reflex edemas).

EDEMAS DUE TO VENOUS THROMBOSIS

During the active stage of any deep thrombophlebitis, that is the femorohiac form or the form involving the lower part of the leg, there usually is marked edema (by contrast with thrombosis in the superficial veins, which rarely causes any swelling). Such edema can partly be explained as due to elevated venous pressure, the lymphatics being normal but unable to carry off the enormous transudate of tissue fluid. But this is not the whole story. In many instances of femorohiac

1 Cystic lymphangiomas, almost peculiar to the root of the neck, are entirely different from the lymphedemas of the limbs and are not included here.

thrombophlebitis there is present about the great artery and vein in the groin and along the pelvic brim an active inflammatory exudate which covers everything in the vicinity. It undoubtedly engulfs the principal lymph trunks, which course about great blood vessels, and so may add lymphatic obstruction to the excessive edema caused by the venous stasis. How much edema results from this cause is difficult to say. By some it is regarded as of great importance. Others belittle it and attribute such edema as is not due to elevated venous pressure to reflex vasospasm occasioned by irritation of the plexus of nerves which surrounds the thrombosed vein and its companion artery. That a peripheral vasospasm is often associated with femoriliac thrombophlebitis and actually occasions edema or at least prevents its relief is attested by Leriche's² treatment of this disease by procaine block of the lumbar portion of the sympathetic nervous system. He asserts, and Ochsner and DeBakey³ confirm his observations, that such an injection repeated over a number of days, relieves discomfort and causes the edema rapidly to disappear.

It must, then, be supposed that the most serious swelling of the lower limb⁴ is due to the edema of combined venous and lymphatic obstruction reinforced by peripheral vasospasm. Such a swelling is occasionally remarkably persistent (fig 2 A). If a collateral venous circulation is slow to develop and if the lymphatics are unusually crippled, it may remain present in some degree for months or years or even throughout life. Its tendency, however, is to diminish with time, especially if the disease has been treated from the beginning by elevation of the swollen limb above the body and by measures capable of relieving such peripheral spasm as may be present. It is particularly important that during the gradual resumption of active use the leg should be protected by elastic pressure. Prolonged lymph stasis leads to fibrosis and to further crippling of the drainage system, a vicious circle. Moreover, in rare instances a causalgia-like state, marked by cyanosis, edema and perhaps a hypersensitive skin, may set in (fig 2 B). Under these conditions, a lumbar sympathetic block with procaine hydrochloride temporarily relieves hypersensitiveness and restores a natural color to the foot. Whether lumbar sympathectomy will then be curative or, as Leriche²

2 Leriche, R. The Problem of Osteo-Articular Diseases of Vasomotor Origin. Hydrarthrosis and Traumatic Arthritis. Genesis and Treatment. *J Bone & Joint Surg* 10:492 (Jul) 1928.

3 Ochsner, A., and DeBakey, M. Treatment of Thrombophlebitis by Novocain Block of Sympathetics. *Technique of Injection Surgery* 5:491 (April) 1939.

4 This account leaves out of consideration the rare reflex spasm of the iliac and femoral artery itself, a spasm which altogether shuts off the arterial supply to the limb and so, if continued, leads to gangrene. But in such a case edema is altogether absent.

believes, the great iliac veins must, in addition, be freed from scar tissue and perhaps divided, is not yet clear

Serious phlegmasia alba dolens is followed in many instances by peculiar local indurations and ulcerations of the lower part of the leg (postphlebitic induration and ulceration) Such appear months or

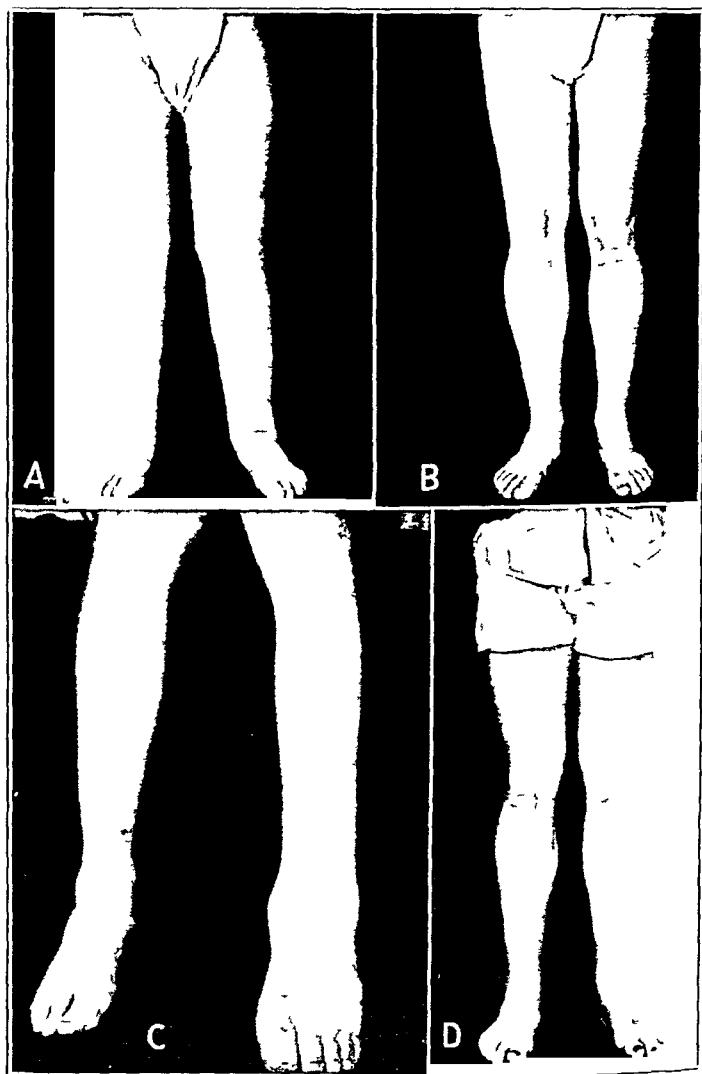


Fig 2—*A*, legs of M C S There is postphlebitic bilateral edema with a possible allergic factor *B* legs of J B T There is postphlebitic edema of the right leg with causalgia-like hypersensitiveness The cyanotic color of the foot is missed in the photograph *C*, traumatic, reflex edema excited by the fall of a block of wood on the foot, subsequently cured by lumbar sympathectomy An allergic factor related to fungi may have been present (From Homans, J *Circulatory Diseases of the Extremities*, New York, The Macmillan Company, 1939) *D*, legs of A J D Allergic edema related to fungi was present The condition was successfully treated by lumbar sympathectomy

years after the original disease and have usually been mistaken for complications of varicosity, which fundamentally they are not. But that they are actually the result of lymph stasis is not clear either and in many instances they certainly are aggravated, if not actually excited, by fungous infection. Treatment of such infection aids in their cure, and sympathectomy influences them favorably, but when especially obstinate and extensive they must be treated by excision and skin graft.

The moderate edema occasioned by thrombosis in the great venous plexuses among the muscles of the calf is peculiar. It is confined to the lower part of the leg and when the patient is up and about is associated with some degree of cyanosis. Several days of elevation of the limb in bed causes it to disappear completely, but it returns on the resumption of an active life. I have elsewhere described this disease, which is distinguished by the alternations just described and by a sense of discomfort in the back of the upper part of the calf on forced dorsiflexion of the foot. Owing to the tendency of the thrombosis to grow into the femoral vein as a loose, propagating clot, it is a frequent source of fatal pulmonary embolism.

ELEPHANTIASIS

According to the manner in which elephantiasic edema makes its appearance, there are several varieties. In none of them, however, is the means by which lymphatic drainage is abolished at all well understood. Operative intervention introduces the surgical sort, filarial infection usually brings on the tropical sort, but the cause of the sporadic and familial varieties is utterly obscure. The end results of all are much the same. The lymphatic system of the elephantiasic limb is entirely destroyed, that is, no valved lymphatics are left and fluid drifts through the interstices of the subcutaneous tissues, some of which may present the appearance of dilated lymph spaces, by gravity alone. No lymph nodes are seen.

In the tissues superficial to the muscular aponeurosis the retained tissue fluid acquires, as the years go on, a large percentage of protein, a proportion sometimes so high as to be more than half that of blood serum—4 per cent in exceptional cases. Probably this proteimized fluid acts as a tissue culture medium and encourages fibrosis. In any event, the tissues become steadily firmer and the skin coarser, thicker and often hairy. Some limbs preserve their shape though there is usually sagging of the skin over the line of the shoe, but in others the skin gives way here and there, forming bizarre deformities, great folds and pouches. From any scratch or prick a clear, pale yellow fluid runs freely until the scratch heals. Healing, in fact in such limbs is usually normal, the blood supply being abundant.

The tissues beneath the aponeurosis, that is, the muscles remain entirely unchanged, a sign that the muscles themselves are not drained

by lymphatics but by capillaries alone. The elephantiasic leg is, of course, unwieldy, yet seems to suffer no muscular deterioration. However, there is no support for Kondoleon's⁵ plan of introducing the fluids of the superficial tissues among the muscles. Even if that could be done, it would presumably embarrass the muscles without improving drainage.

The febrile attacks to which the elephantiasic limb is subject are more common in tropical countries than elsewhere but may set in, without apparent reason, in the sporadic elephantiasis of temperate climates. After a preliminary period of discomfort, which in the filarial form of the disease is often marked by localized pain and tenderness the entire limb becomes swollen and its surface red and hot. A chill is rather common, after which the temperature rises rapidly to 102 or 104 F and the patient is greatly prostrated. Indeed, the illness may appear dangerous, but actually the attack is self limited, subsiding in three to five days. Though it has often been supposed that the infection is streptococcic—it should never be called "lymphangitis," since there are no lymphatics left—Drinker and Field were the first to prove it to be such in the experimental animal. Actually, in their observations the attacks started automatically, and the streptococci could be recovered for only a few hours near the height of the attack. This explains the difficulty of finding the causative organisms in human beings. A brief account of these experiments is included in papers on the general subject of elephantiasis by Drinker, Field and me.⁷

The fungi of the skin may also be concerned with these explosions, though perhaps only indirectly. For example, an active young man suffering from elephantiasis with attacks so frequent and severe that he had become an invalid was so far relieved by a plastic operation that for two years he remained well. Finally, however, during hot, damp summer weather, an old epidermophytosis recurred and a bad attack of elephantiasis followed. Probably streptococci entered the tissues, as they so often do, via the cutaneous lesion, though it is conceivable that the attack was allergic. Vigorous treatment subdued the epidermophytosis, and the trouble has not been repeated.

Surgical Elephantiasis—This form affects most often the arm following operations for cancer of the breast. It may occasionally

5 Kondoleon, E. Die operative Behandlung der elephantiasischen Oedeme. *Zentralbl f Chir* **39** 1022, 1912.

6 Footnote deleted.

7 Homans, J., Drinker, C. K., and Field, M. E. Elephantiasis and the Clinical Implications of Its Experimental Reproduction in Animals, *Ann Surg* **100** 812 (Oct.) 1934. Drinker, C. K., Field, M. E., and Homans, J. The Experimental Production of Edema and Elephantiasis as a Result of Lymphatic Obstruction, *Am J Physiol* **108** 509 (June) 1934.

appear as a late complication of malignant disease in the pelvis, whether treated by operation or by irradiation. It may also result from lymphosarcoma in the groin or axilla, especially when an operation has been performed and the part subjected to irradiation.

Elephantiasis of the arm as a complication of mammary cancer occurs in a very freakish way. An axillary dissection alone, in the event of a mistaken diagnosis of cancer, is capable of producing it, though not in the serious form due to axillary metastasis plus operation and recurrence.

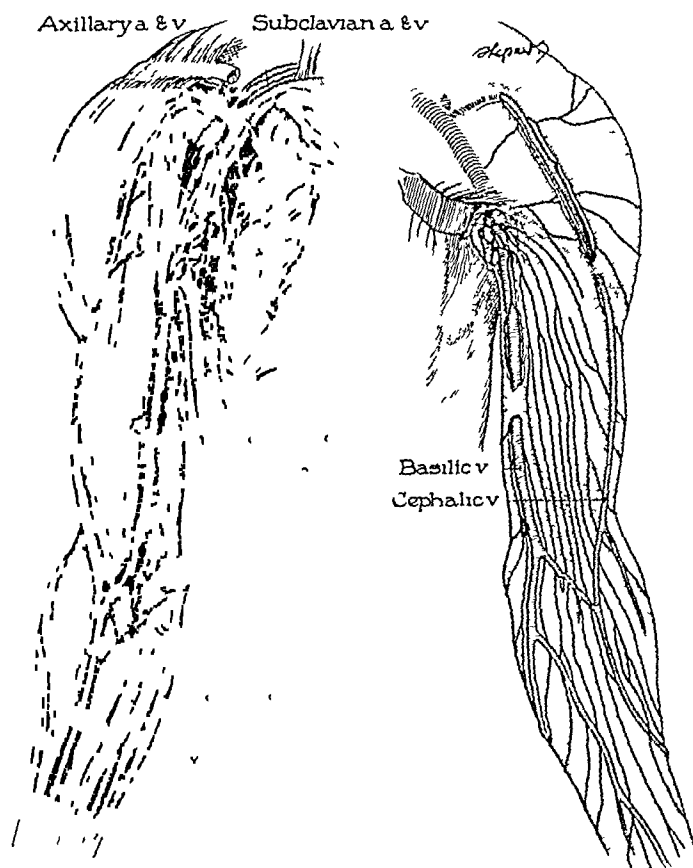


Fig 3—Lymphatics of the arms. In the left arm some of the superficial lymphatics are shown. They enter the axilla with the basilic vein. In the right arm, the deep (perivascular) lymphatics of the forearm, arm and axilla are represented. They are closely related, as in the leg to the artery rather than to the vein. Rouviere's descriptions have in the main been followed.

Recently, Veal¹ has found that there are a pure lymphatic variety of sort due to venous obstruction and a mixed type. So far as the lymphatics are concerned it will be recalled that most of the small vessels

¹ S. Veal, J. R. The Pathological Basis for Swelling of the Arm Following Radical Amputation of the Breast. *Surg. Gynec. & Obst.* 67:752 (Dec.) 1938.

of the skin and subcutaneous tissues of the hand and arm come together and enter the axilla at the spot where the basilic vein perforates the aponeurosis. Here they can readily be interrupted, but after entering the axilla they are more closely related to the axillary artery than to the vein. Thus they are not particularly exposed in the axillary dissection proper. Moreover, a variable amount of lymphatic drainage passes through the lymph nodes at the elbow and so along the brachial and axillary arteries. Thus, an axillary dissection may well leave the lymph drainage system intact unless most of the superficial vessels are divided in making the skin flap or unless axillary metastasis is extensive.

In some cases, evidence that the axillary dissection has interrupted many lymphatics is offered immediately after operation by a collection of clear lymph in the wound. Even then the fluid often finds a way. Swelling may occasionally appear and disappear, or perhaps remain moderate, a matter explainable on anatomic grounds. However, once well marked surgical lymphedema sets in, typical elephantiasis usually develops, with the characteristic induration and thickened skin and even the febrile attacks.

The treatment of surgical elephantiasis is, first and foremost, elevation of the part. The arm should be kept horizontal or raised on a pillow when not in use. It is even possible to devise means of suspending it at night. Exercise, in moderation, is rather good for it than otherwise. In fact, fluid can escape from the arm only by gravity or by being forced through the tissue spaces. Plastic operations are difficult and unsatisfactory. For the most fully developed sort, amputation is the best remedy provided the patient has a moderate life expectancy.

Filarial Elephantiasis—Not all persons having filarial infestation suffer from elephantiasis. Indeed, O'Connor, Golden and Auchincloss,⁹ with the aid of the roentgen rays, have demonstrated numbers of calcified worms in the tissues in the absence of any edema. But once the lymphatics are crippled, the tropical disease is more serious than that of temperate regions, because, as Matas¹⁰ has pointed out, the patient is exposed to so many infections. Febrile attacks are common, and doubtless the tissues often permanently harbor bacteria which make surgical treatment difficult. Auchincloss¹¹ has attempted to excise as much infested

9 O'Connor, F. W., Golden, R., and Auchincloss, H. Roentgen Demonstration of Calcified *Filaria Bancrofti* in Human Tissues, *Am J Roentgenol* **23** 494 (May) 1930.

10 Matas, R. The Surgical Treatment of Elephantiasis and Elephantoid States Dependent upon Chronic Obstruction of the Lymphatic and Venous Channels, *Am J Trop Dis* **1** 60, 1913.

11 Auchincloss, H. A New Operation for Elephantiasis, *Porto Rico J Pub Health & Trop Med* **6** 149 (Dec) 1930.

subcutaneous tissue as possible, with the idea of removing focal spots whence outbursts of infection may come. However, the real value of such a procedure probably lies in the removal of a large amount of fluid-holding unhealthy tissue between the skin and the deep structures of the leg, and the modern operation is based on this general plan rather than on any idea of drainage. Such treatment is described in the following section.

Elephantiasis Nostra and Milroy's Disease—Sporadic elephantiasis (elephantiasis nostra) is the rather common form which crops out here and there without known cause. Its nature and behavior differ in no way from those of the familial sort, to which Milroy's^{12a} name is usually attached. Strangely enough, the family which formed the object of Milroy's^{12b} study suffered from a disorder not only inherited but congenital, that is, almost all the members were affected in infancy. Meige¹³ described a family in which the disease usually developed, as does the sporadic form, near puberty or soon after. Hope and French¹⁴ have discovered another instance of this sort.

The cause of sporadic and familial elephantiasis is utterly unknown. Why should a person whose legs from birth to the age of 15 or 20 have seemed entirely normal, at that time and without suffering any accident or other physical change, begin to notice a swelling of one or both legs? I¹⁵ have explored the pelvis in several patients hoping to find an obstruction in the large lymph vessels which wind about the great artery and vein of the pelvic brim. In 1 case the lymphatics were thickened and enlarged but not dilated. They carried almost no lymph (probably a little from purely pelvic sources), and the nodes in their course were curious little flattened structures. In the tissues of the elephantiasic leg it is impossible to find anything like a valved vessel, though plenty of large spaces are present, and if a little trypan blue, a dye readily taken up by the lymphatics, is injected deep into the skin it either remains stationary or, if the leg is elevated, can be seen to color the skin in a patchy way, spreading about by gravity. It may flow from ankle to knee in as little as fifteen minutes, but this occurs only if there are unusually abundant cutaneous spaces. In fact the tissue fluids flow up or down according as the leg is elevated or depressed but, having reached the body, appear to be rapidly absorbed.

12 Milroy, W. F. (a) An Undescribed Variety of Hereditary Oedema. *New York M. J.* **56** 505 (Nov. 5) 1892. (b) Chronic Hereditary Edema. *Milroy's Disease*, *J. A. M. A.* **91** 1172 (Oct. 20) 1928.

13 Meige, H. Dystrophie oedémateuse héréditaire. *Presse med.* **6** 341 (Dec. 14) 1898.

14 Hope, W. B., and French, H. Persistent Hereditary Oedema of the Legs with Acute Exacerbations. *Quart. J. Med.* **1** 312 (April) 1908.

15 Homans, J. The Treatment of Elephantiasis of the Legs. *New England J. Med.* **215** 1099 (Dec. 10) 1936.

The general account of elephantiasis already given sufficiently fits the behavior of this particular disease. Both legs are enlarged in a fair number of cases, and in that event the external genitals as well may be involved. There is really no limit to the amount of enlargement or deformity, but evidently the tissues drain better in some instances than in others, so that certain elephantiasic legs never attain great size. The febrile attacks seem to occur only in the cases of more serious involvement, but actually their onset is unpredictable.

Treatment—Palliative measures are not to be despised. Should the tissue fluids drain from the leg rather rapidly when it is elevated, a balance may be found between rest and use—so many hours up and so many down. The shoe prevents enlargement of that part of the foot which it covers, and an elastic stocking worn from toes to knee may, with the aid of exercise and elevation, permit a good deal of dependency. At night the foot of the bed should be raised, perhaps 6 inches (15 cm), for it is during the sleeping hours that the best drainage is secured. By such means an occasional patient is able to control the disease.

The plastic operation aims, frankly, to do nothing more than remove the tissues in which fluid accumulates. By turning back broad flaps which include the aponeurosis and exposing bone, muscle and tendon sheaths, half the circumference of these deep structures can be laid bare at one sitting. Then the lymph-soaked fibrous tissue and sclerosed fat are cut from the deep surface of the flaps, which are left very thin. Indeed, it is probably best that these for two thirds of their width should be made of whole skin alone, a little fat being left near the base for purposes of venous drainage.¹⁶ The incision for the first stage of the plastic operation is best made on the anterointernal face of the leg (fig 4). Near the knee it becomes a broad Y, and at the internal malleolus, an unequal, inverted Y with a long arm forward. The difficulty with the blood supply of the flaps is not arterial but venous, that is, they receive enough blood but drain badly, and it is worth while to spare as many perforating veins as possible toward the base of each flap. Perhaps those who are accustomed to dealing with whole thickness skin grafts would do better to use these instead of flaps. However, if one scores the skin just before closing and makes firm, even, elastic pressure, very little sloughing occurs.

Each operation is carried out in a bloodless field by the aid of an Esmarch bandage applied to the thigh and reenforced if necessary with

16 A very interesting suggestion has recently been made to me by Dr R H Smithwick, namely, that after a lumbar sympathectomy has been performed the flaps should be made of whole skin alone for their entire width. Dr Smithwick reports that he has tried this procedure with success.

rubber tubing. Otherwise the operation is hopelessly bloody, and needless to say the control of bleeding after the removal of the constricting rubber bandage is no easy matter. The only nerve which seems worth sparing is the sural, since this supplies the outer side of the foot and

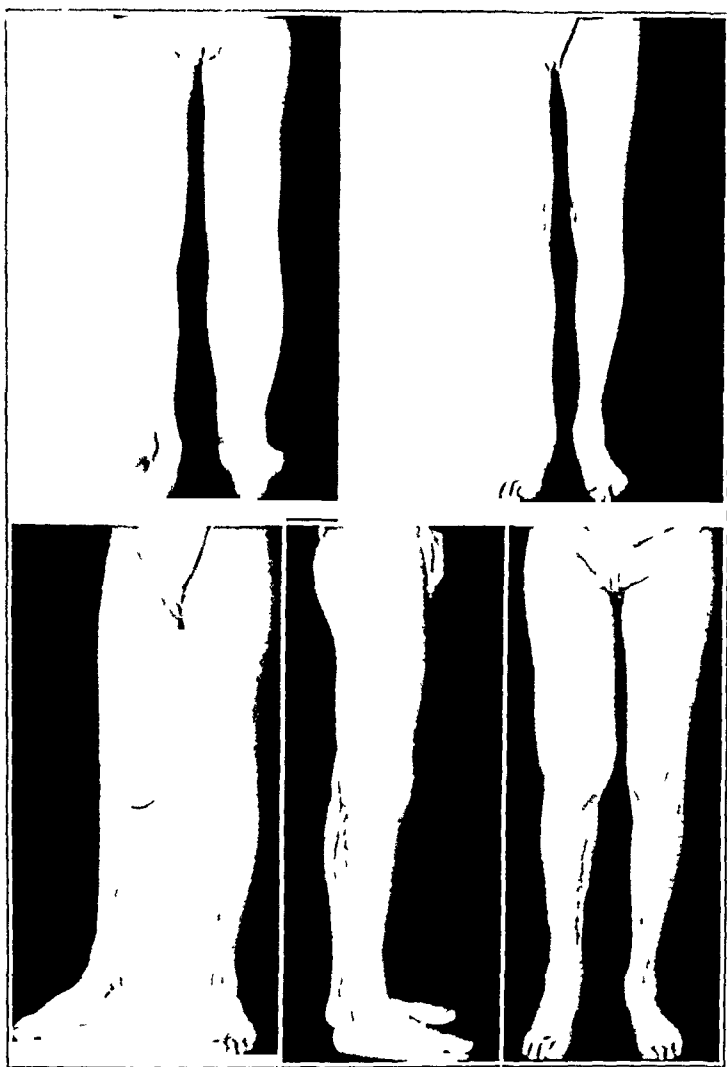


Fig. 4—Legs of M. A. B., a patient with elephantiasis nostras. The lower photographs illustrate successively, from left to right, the immediate result of the first plastic operation, the immediate result of the second plastic operation and the end result (at this time the patient was wearing an elastic stocking).

heel. Curiously enough, patients do not seem to object to the numbness of the leg. There is no danger of disturbing the nerve supply of the sole, toes and much of the foot.

The plastic operation which treats the second half of the leg must of course, be postponed for several months after the first operation, otherwise the last two flaps could hardly be left back to back with the first ones. It will be observed that the foot, so far as it requires treatment, is fairly well reduced in size by the procedures described, but some thickened tissue is apt to be left in the midline from instep to toes. If necessary, this can be removed at a third operation, and any broad or hypertrophied scars, if such are present can also be excised. At this time skin grafts may be useful, especially if infection or unsatisfactory healing is feared.

In cases of very serious involvement, when the sacculated parts are ulcerated and presumably infected, the plastic operations just described are not appropriate. Flaps made under these conditions are likely to slough, and infection is implanted on the hitherto uninvolved deeper parts. It will therefore be safest to excise great masses of tissue, including the underlying aponeurosis, without any flap making whatever. Then, after antiseptics have been applied for ten days or so, the clean, newly granulated surface can be covered with an Ollier-Thiersch or even a full thickness skin graft. I have recently carried out such a procedure successfully in the case of a man whose huge, deformed leg the scene of innumerable febrile attacks, had worn him down and made an invalid of him (fig 5).

REFLEX EDEMAS

These states are variously known as trophic edema and traumatic edema. They are related to causalgia and indeed are usually associated with so much hypersensitiveness of the skin as to deserve that name. They range from the terrible state of hypersensitive skin and burning pain described by Mitchell and his co-workers,¹⁷ in which edema is trifling, to great swellings of a limb in which pain and sensitiveness to touch are perhaps little marked. It is proposed here not to discuss causalgia or the entire subject of the post-traumatic pain syndrome but to indicate how the traumatic edemas can be recognized.

Actually, reflex edema probably represents a dysfunction of the nervous mechanism associated with the blood vessels. The little nerves of this mechanism—whether they are purely vasomotor and therefore sympathetic or are sensory and therefore belong to the somatic nervous system—are carried on the blood vessels into the great nerve trunks and so injuries of nerves as well as of blood vessels may throw

¹⁷ Mitchell, S W, Morehouse, G R and Keen, W W. *Gunshot Wound and Other Injuries of Nerves*, Philadelphia, J B Lippincott Company, 1864.
 Mitchell, S W. On a Rare Vasomotor Neurosis of the Extremities, and on the Maladies with Which It May Be Confounded, *Am J M Sc* 76 17 (July) 1878.

them into disorder. Strangely enough, any one of a great variety of traumas, in the broad sense, may be the exciting factor. A block of wood falls on the foot (fig 2C), a wound by a thorn or by the bite of an animal becomes mildly infected, femorotibial thrombosis occurs

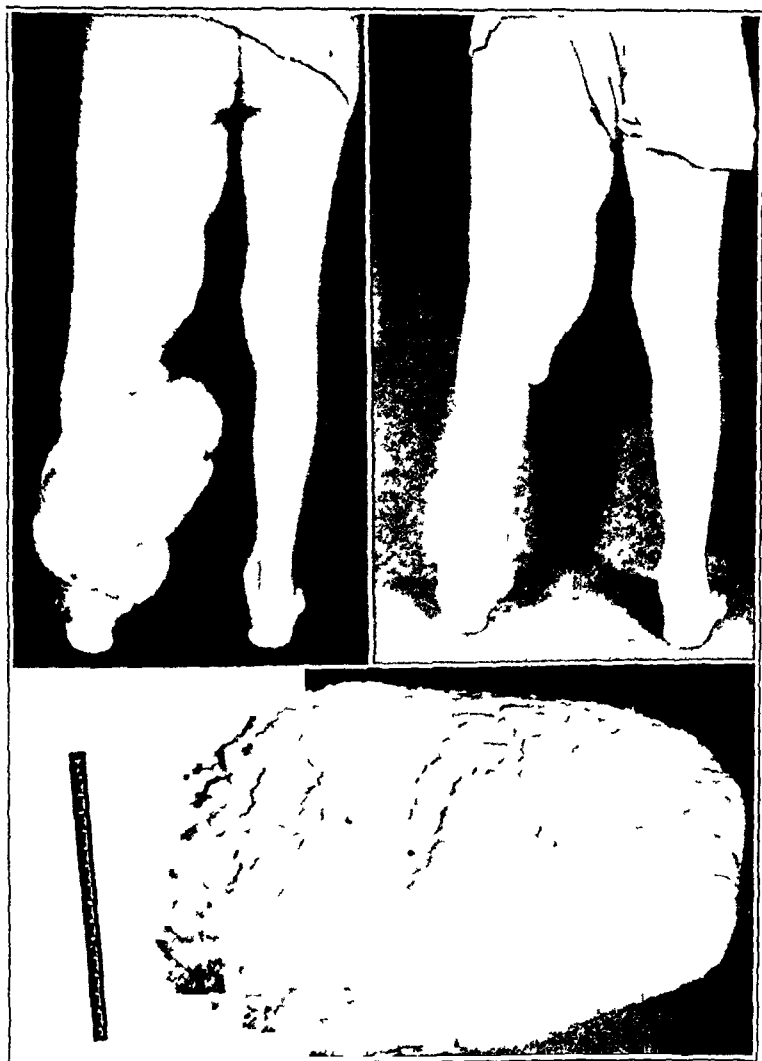


Fig 5—Photographs in the case of H. F. W., a patient with advanced elephantiasis nostra. There were disabling febrile attacks. The tissues were permanently infected. The whole back of the leg, the seat of a great local enlargement, was cut away. The subaponeurotic area exposed by the excision was covered with a thick Ollier-Thiersch graft. The attacks have been controlled, but further plastic procedures will be required.

(fig 2B) or a Colles fracture or its reduction injures a median nerve, then the foot or the hand, the whole leg or arm, as the case may be,

becomes swollen, partly paralyzed and partly held immobile from fear of contacts, the bones atrophied and the skin pale or red and as a rule thin and hypersensitive

All such changes appear to be due to a sensory-sympathetic reflex which begins in the sensitive nerves of the blood vessels already described, passes inward to make a connection with outgoing sympathetic fibers and finally travels peripherally in the form of an unnatural sympathetic impulse. Whether the impulse must pass through a segment of the cord and thence out through a sympathetic ganglion or may go no farther centralward than a plexus on a large artery is immaterial. It is enough to know that it can almost always be broken by interrupting the sympathetic nerve supply to the affected limb by a paravertebral sympathectomy and that it can often be broken by Leriche's¹⁸ periaxillary sympathectomy, as of the brachial artery for edemas of the upper limb.

Those who see much of accident and liability insurance matters will realize that these reflex edemas and the related states of painful and hypersensitive limbs offer a serious problem. Many of them are transitory, a few are persistent and all are more or less under the influence of the patient's mental reactions. Perhaps the most generally useful way to manage them is to accept Leriche's view that the sympathetic system is concerned with all pain¹⁹ (and much edema) and to make use of procaine block in studying the individual case. Livingstone²⁰ discussed such matters in a most informative way. I prefer a paravertebral sympathetic block with procaine hydrochloride to local injection of the anesthetic on the ground that if, as almost invariably happens, paralysis of the sympathetic nerves restores normal sensibility, color and warmth to an extremity, the patient is convinced that normal conditions have for the moment been restored, the ordinary sensibility to touch, pinprick etc., being present, thus a favorable reaction to a sympathetic block.

18 Leriche, R. Des regles a suivre dans le traitement des fractures articulaires par infiltration novocainique des ligaments et mobilisation active immediate, *Presse med* **45** 873 (June 12) 1937

19 To one who finds the sympathetic system concerned with many painful states, it is confusing to read Sir Thomas Lewis' observations on the "nocifensor nerves" and their activities (Lewis, T. The Nocifensor System of Nerves and Its Reactions, *Brit M J* **1** 431 [Feb 27], 491 [March 6] 1937). These he found to be entirely different from the ordinary sensory nerves, though actually they pass through the posterior nerve roots. They have the property of distributing superficial tenderness in response to local injury and when stimulated centrally cause capillary vasodilatation. But all this is perhaps not related to reflex edema.

20 Livingstone, W. K. Post-Traumatic Pain Syndromes. An Interpretation of the Underlying Pathological Physiology, *West J Surg* **46** 341 (July), 426 (Aug) 1938

will often whether or not the block is repeated start the patient on the road to improvement. If not, a permanent operative sympathectomy may be used. Cures also result from perianterial sympathectomy, presumably because the incoming impulses of the reflex are interrupted by the procedure.

Allusion has been made earlier (in the section devoted to the edema of disuse and injury) to the edema of sprains. Following the teaching of Leriche²¹ various attempts have been made to break up with the aid of local injections of procaine hydrochloride (especially in the case of sprained ankles, the vicious edema-producing vasomotor reflex which he describes. Some of these have been encouraging (Moynahan²²), but there is as yet no substantial agreement on the subject.

EDEMAS DUE TO ALLERGY AND INFECTION

These two causes are placed together because as the following discussion will show it is not always easy to distinguish one from the other and indeed the two may be combined. Occasional patients infected with the common fungi of the feet suffer from outbreaks of allergic redness and swelling, attacks which pass off rapidly but which may, in a cumulative way, lead to chronic edema (figs 2D and 6C). It is often difficult to say in any given case whether the attacks are actually due to hypersensitiveness or to secondary infection entering the skin by way of the lesion caused by the fungus. In the latter event, the infection almost necessarily streptococcic, takes the form of lymphangitis perhaps both diffuse and tubular, and in this way damages the superficial tissues and cripples the lymph channels. One would suppose that an accurate account of the attacks might distinguish between these causes but patients are not always reliable observers, and by the time a leg is enlarged and indurated, even ulcerated, the course of the disease can seldom be traced. It was formerly believed that infection entering by way of sores or abrasions was capable, by repeatedly introducing bacteria into the tissues, of leading in time to chronic edema, but it is my impression that fungous infection is a more potent cause. The matter is especially confusing because so many chronically swollen and indurated legs are prone to ulceration anyway, as a result of scratching and accidental trauma.

The following is a case in point.

CASE 1—I P, an obese woman 36 years of age, had suffered after childbirth from a phlegmasia alba dolens of her left leg, from which she had recovered with only a little residual edema. However, it was the right leg which afterward became elephantiasic, and there may, of course, have been an unnoticed thrombophlebitis on

²¹ Moynahan, E. J. Treatment of Acute Sprains by Procaine Infiltration (Leriche's Method), *Brit. M. J.* **1** 671 (April 1) 1939.

that side. In any event, sores appeared in the lower half of the right leg, and severe inflammatory attacks attended by high fever occurred at intervals of several months (fig 6 *A* and *B*). During every attack the whole right leg became red and swollen. After each, desquamation occurred. The ulcers were uncontrollable. Epidermophytosis on the foot was unmistakable. Since no treatment which the patient was capable of carrying out caused the ulcers to heal or the attacks to cease, a lumbar

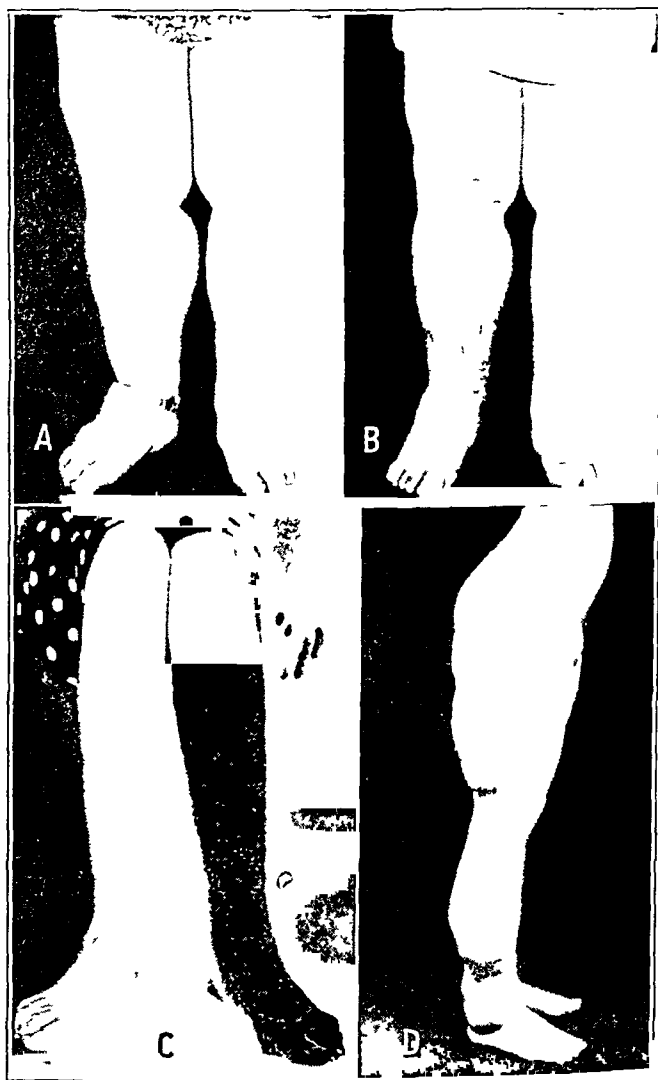


Fig 6—*A*, legs of I P, a patient with edema due to allergy and infection, so permanent as to deserve the name of elephantiasis. Extensive multiple ulcerations are present. *B*, legs of the same patient during a febrile attack (infectious or allergic). *C*, legs of T H, a patient with allergic edema related to fungi. *D*, legs of R N M, a patient with a cavernous lymphhemangioma. Vicarious menstruation occurred from the small dark spots above the knee. (The individual photographs are taken from Homans, J. *Circulatory Diseases of the Extremities*, New York, The Macmillan Company, 1939.)

sympathectomy was performed. The idea behind this operation was to change the environment of the organisms by increasing the vascularity of the superficial parts and so to cause the ulcers to heal. Actually the effect produced was to leave the skin so hot and dry that a condition hostile to fungi was created. At the time of writing some two years later, only one small ulcer remains; no more attacks have occurred and the leg is distinctly smaller and less hard than before.

The second case to be described is perhaps one of a pure allergic reaction to a fungus though this is by no means certain especially because as already explained allergic or infectious outbreaks may occur in sporadic elephantiasis in the presence of infection by fungi.

CASE 2.—L. R., a small woman 30 years of age, had attended a gymnasium some eight years earlier and was aware of having acquired a fungous infection of her feet. Two years later, six years before she came under my observation, the lower part of the right leg rather suddenly swelled and a month afterward the whole leg below the knee became "sore." She went to bed for three weeks. Since that time she had suffered several such attacks and three weeks before she was first seen by me she noticed an increase of swelling so severe that the leg felt "as if it would burst." She had noticed also two irritated areas, one over the instep and the other on the shin near the knee. When examined, the skin of the right foot and leg was a little hot and faintly reddened but since the patient had kept the foot elevated for several weeks, the ankle and calf were only slightly swollen.

About a year and a half later, after a summer vacation during which the leg gave almost no trouble, she suffered the worst attack she had ever experienced. This time both legs swelled acutely. She noticed some tiny blisters on both feet. After a week of swelling, the legs returned to their previous state. Now, the right leg is clearly the seat of chronic edema and slight but noticeable deformity. There is no external sign of epidermophytosis. The patient's hyper-sensitiveness to fungus is under investigation.

Treatment—The problem of dealing with allergic states especially those due to an elusive fungus, is difficult. The patient's reaction to her own fungus should of course be studied, but when no desquamating skin and no thickenings between the toes are present this cannot be done. One must then fall back on a "shotgun" collection of fungi, test with that and if necessary desensitize the patient to the whole group.¹

I use another method—lumbar sympathectomy. I am not aware that this procedure has before been used to cure epidermophytosis. However, the hot, dry skin of full peripheral vasodilatation is obviously hostile to the growth of a fungus, and the one experience cited here (case 1) is decidedly encouraging. It hardly seems right to recommend lumbar sympathectomy for routine use, for it certainly carries a risk, which in the presence of infection in the corresponding leg may be prohibitive. Probably it should be used only after prolonged treatment of any (bacterial) infection which may be present, in carefully selected cases.

CAVERNOUS LYMPHANGIOMA

A brief account of this peculiar deformity is offered so that comparison can be made with the various states of elephantiasis described. It is of course a congenital malformation. The superficial tissues in the region affected are puffy, presenting a surface which may be smooth or slightly uneven, but the color of the skin is normal. The enlargement may involve a whole foot or hand or only a finger or two.

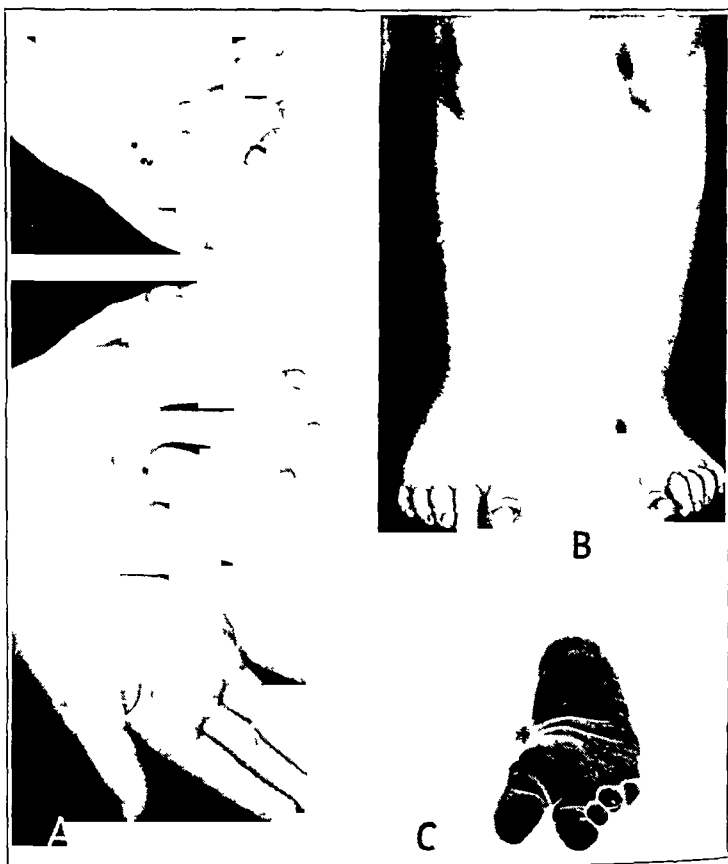


Fig 7—*A*, hands of R F A. The left hand shows a bizarre malformation. The right hand, which has been photographed from both the dorsal and the palmar aspect, shows a diffuse cavernous lymphangioma and has already been subjected to one operation. *B* legs of J B A, a patient with a cavernous angioma of the right foot. *C*, cavernous angioma at the base of the great toe of G. Huge, deformed toes were associated with the angioma. (The individual photographs are taken from Homans, J. *Circulatory Diseases of the Extremities*, New York, The Macmillan Company, 1939.)

The part feels rather boggy and not tense, and the swelling is little affected by elevation or depression. It does not pit like an early edema. Yet if one sees an infant's foot like the one shown in figure 7, one can

hardly be certain save by the march of events, whether the trouble is *one of lymphatic deficiency the superficial parts being otherwise normal*, or whether the tissues superficial to the muscular aponeurosis are malformed. In the first case, the whole leg will present lymphedema and will slowly enlarge. In the second the change will remain confined to the original area and will only enlarge with growth. Not uncommonly the lymphangiomas of infancy are associated with bizarre malformations of the fingers or toes (fig 7 *I, B and C*).

A cavernous lymphangioma often occupies several dermatomes on the surface of a limb, in extreme cases, the whole limb, as is shown in figure 6 *D*. It must be recognized that the superficial tissues are totally changed. They are fluid soaked, fibrosed and very vascular. The aponeurosis beneath may be lacking so that the abnormal tissue may extend in an irregular shallow way into the muscle. Thus the removal of the larger lymphangiomas is a difficult matter. It is usually best to remove one bit by bit in a series of minor procedures, especially when it occupies a hand or a foot.

COMMENT

An attempt has been made to sort out and describe the lymphedemas, of the lower limbs especially, which are due to local causes. The elephantiasis, that is, those associated with a total disappearance of the lymph vessels, are unexplainable and, as one might suppose, are really incurable. That is to say, there is no way of restoring drainage of the tissue fluids. To do away with the swelling, one must remove the tissue in which fluid collects. *This need not, as a rule, be done for the thigh.* It is enough to reduce the size of the leg below the knee.

None of the other lymphedemas are wholly of lymphatic origin. Those which originate in femorofemoral thrombophlebitis are certainly due in part to involvement of the larger lymph vessels of the pelvic basin in the perivascular exudate which is so often present in these cases, but venous obstruction (at first) and peripheral vasospasm (later) certainly contribute to the swelling of the limb.

The allergic edemas are undoubtedly going to prove of increasing clinical importance. As yet it is not known whether such states can become established without definite acute attacks of redness, swelling and fever. If edemas of this sort can arise quietly, as it were, then the various fungi of the skin must be even more common and have more access to the internal mechanism than is now believed to be the case. Without proposing to be an alarmist, I deprecate the rather general tendency of members of the medical profession to shut their minds to this matter.

The reflex edemas, that is, the rare and picturesque swellings which arise unpredictably from trivial injuries and infections, seem to be related

to sympathetic control of the peripheral blood vessels. However, their peculiar mode of origin, especially in trauma to certain nerves (the median and sciatic) should make one careful not to be too certain of their nature, and the hypersensitiveness to touch which is so often associated with them appears to give them a relation to the causalgias. There is much to be learned of the relation of pain, superficial tenderness and edema, as a complex, to the somatic and sympathetic nervous systems. The reflex pathways concerned with the reflex edemas and causalgia-like states require especial study.

AMPUTATION FOR PERIPHERAL VASCULAR DISEASE

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In spite of significant additions to the conservative therapy of peripheral vascular disease such as suction and pressure therapy, intermittent venous hyperemia, iontophoresis with acetylbetamethylcholine hydrochloride (mcholy) and other measures (the value and limitations of which have been recently analyzed from this clinic¹), there still remains a group of cases in which amputation must be performed either as a life-saving measure or to rid the patient of a painful and functionless limb which undermines his morale and lowers his earning capacity. It has seemed to us that since the advent of the newer conservative measures, which are urged and demanded by patients even in obviously hopeless cases, patients come later than ever for amputation, thereby increasing the mortality and discrediting the procedure.

In this brief study we wish to present our experience with major and minor amputations done for peripheral vascular disease by ourselves or under our supervision in the five year period from 1933 to 1938. The purpose of this presentation is to emphasize certain procedures which have helped us to establish the indications, to decrease the mortality associated with amputation and to improve the functional status of the patient.

INDICATIONS FOR AMPUTATION

No surgeon has the right to deny the chance for life to a patient, even if the risk is great. The patient's relatives may say that they would rather see him die than lose his leg. There is usually, however, much less opposition from the patient than from the relatives, and if the surgeon convincingly urges amputation the percentage of refusals will not be great.

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1 de Takats, G., Beck, W. C., and Roth, E. A. The Neurocirculatory Clinic I. Peripheral Vascular Disease, *Ann Int Med* **13** 957 (Dec.) 1939.

By a "fair chance to save the limb" we mean the following conditions (1) ability of the patient to have absolute rest in bed and adequate nursing care for approximately three months, (2) absence of any sign of spreading infection (which would indicate immediate amputation), (3) absence of massive gangrene (small gangrenous patches, or true cutaneous infarcts, may slowly fall off and epithelize), and (4) absence of intractable pain or good response to absolute rest, proper postural angle, vasodilators, mild sedatives, passive vascular exercises or paravertebral block with alcohol. When these conditions are not fulfilled, an early amputation lowers mortality, restores the patient's morale and may restore some of his earning capacity.

The last-mentioned benefit should be considered in regard to weight bearing. Most patients above the age of 60 will not learn to use an artificial limb, and a weight-bearing stump need not be considered. Because existence in a wheel chair is dreaded by every one, we wish to present the following case history.

REPORT OF A CASE

Mrs E N, 69 years old, diabetic, was suffering from a popliteal atheroma. Although she had no frank gangrene, severe ischemic neuritis was present and was so intractable that an amputation was suggested. It was readily consented to. A Callander amputation was done on March 7, 1938. Twelve days after the operation the patient was walking on crutches. On her discharge from the hospital she was put on a 1,500 calory diet for control of the diabetes, and it was not expected that she would learn to use an artificial limb. However, she appeared in the office three months afterward with an excellent weight-bearing stump, using an artificial limb without a cane or crutches. She was the oldest patient in this series who learned to use an artificial limb.

DETERMINATION OF THE PROPER LEVEL OF AMPUTATION

In a previous communication one of us (de Takáts²) pointed out that although the pulses and the color of the limb point to a probably satisfactory level of amputation, the literature contains many reports of reamputations at a higher level which were undertaken because of sloughing of the skin or of the muscles. Our clinic has consistently utilized measurement of cutaneous temperatures and production of histamine flares to determine the level of circulatory efficiency. The patient's lower limbs are exposed to room temperature for fifteen minutes, and the abdomen is heated with a heat cradle to release the vasospastic element. Often a sudden drop in temperature is felt at a certain level, which is then marked with an indelible dye. This level

2 de Takats, G. The Determination of the Proper Level of Amputation, *Internat J Med & Surg* 47:339 (Sept) 1934.

may be a few inches below the hip joint, just above the knee, at the knee or at the midcalf, often in cases of infectious diabetic gangrene the entire leg and foot are warm. Such a finding, as was emphasized by McKittrick and Pratt,³ permits minor amputation (of toes), which heals well even in the presence of diabetes and in the absence of palpable pedal pulses. Of course, if the pulses of the foot are well palpable and spreading infection is absent, a digital or arteriolar obstruction is obviously present, and minor amputation or spontaneous separation (to be discussed later) is preferable.

The cutaneous temperatures can be determined by a simple mercury thermometer adapted to such use, but when this is not available the palm is capable of detecting sudden drops of temperature. If the fall in cutaneous temperature is gradual, there is really no definite borderline of circulatory efficiency.

Histamine flares are produced by injecting 0.1 cc of histamine hydrochloride or histamine acid phosphate in a 1:1,000 solution. Ampules containing this amount are readily obtainable on the market. From four to five injections are made, at the usual sites of amputation, such as the midthigh, the lower part of the thigh, the knee, a point 7 inches (17 cm) below the knee and the dorsum of the foot. A great deal of edema and cyanosis and the pressure of spreading lymphangitis obviously prohibit the use of these injections at the site of the complications. The reaction of the skin to histamine is read in five minutes by determining the size of the hyperemic zone and the intensity of hyperemia or by measuring the rise in cutaneous temperature as suggested by Perlow.⁴ The latter procedure is helpful with Negro patients, in whom the arteriolar response to histamine is not visible. A detailed study of the cutaneous reactions to histamine has been published before.⁵

The two tests, namely, determination of the cutaneous temperatures and production of histamine flares, point to the same level almost invariably. When there is not much time to lose, the histamine flares alone have been utilized.

On the basis of several hundred such determinations we have concluded that a positive reaction to histamine insures a viable skin flap, provided no severe infection or undue tension of skin sutures occurs. A negative reaction to histamine does not exclude the possibility that

3 McKittrick, L. S., and Pratt, T. C. Principles of and Results After Amputation for Diabetic Gangrene, *Ann. Surg.* **100**: 638 (Oct.) 1934.

4 Perlow, S. The Temperature of the Flare as an Index of the Intensity of the Histamine Skin Reaction, *Am. Heart J.* **11**: 605 (May) 1936.

5 de Takáts, G. The Cutaneous Histamine Reaction as a Test of Collateral Circulation, *Arch. Int. Med.* **48**: 769 (Nov.) 1931.

a well healing stump may occur. In fact, some years ago Smith⁶ of New York, demonstrated to one of us his excellent technic of amputation of the lower part of the leg at a level at which the reaction to histamine was negative. His delicate technic and careful attention to minute detail insure wound healing under doubtful circumstances. In our experience, however, this amputation did not result in primary union in the type of patients referred to us for amputation. After amputation at a level at which histamine flares were obtained we have not seen any sloughing. The reason for marginal necrosis will be discussed in the technical part of this paper.

PREPARATION OF THE PATIENT

Patients who are to have an amputation fall roughly into two classes. First, there are the septic, dehydrated patients, who must be prepared with a sufficient amount of fluids, often with transfusions, if diabetes is present the acidosis at least should be controlled.⁷ Because gangrenous parts so often harbor anaerobic bacteria, our standing order is to give two prophylactic doses of polyvalent anaerobic serum. It must be emphasized that a positive culture of *Clostridium welchii* does not mean a clinical infection with this organism, nevertheless, the high mortality of gas gangrene following amputation⁸ (59 per cent for the entire group and 75 per cent for diabetic patients) makes it imperative that the incidence of postoperative gas gangrene should be minimized. There is good evidence now of the value of serum in cases of gas gangrene, both in prophylactic and in therapeutic doses.⁹ In 2 patients of this series fulminating gas gangrene developed. The older, a 65 year old diabetic patient, died, the younger, 45 years old suffering from thromboangitis obliterans, recovered after use of massive amounts of serum, administration of sulfanilamide and wide exposure of the intramuscular spaces. This experience makes us wonder whether the prophylactic dose ought not to be raised to a

6 Smith, B. C. Amputation Through Lower Third of Leg for Diabetic and Arteriosclerotic Gangrene, *Arch Surg* **27** 267 (Aug.) 1933

7 de Takats, G. Surgery in Diabetes, *J. Kansas M. Soc.* **36** 177 (Mar.) 1935

8 Eliason, E. L., Erb, W. H., and Gilbert, P. D. The *Clostridium Welchii* and Associated Organisms. Review and Report of Forty-Three New Cases, *Surg., Gynec. & Obst.* **64** 1005 (June) 1937

9 Bates, M. T. Gas Gangrene. A Review of Thirty-Two Cases with Special Reference to the Use of Serum, Both Prophylactic and Therapeutic, *Ann Surg* **105** 257 (Feb.) 1937. Mitchell, O. W. M., Bryant, T. L., and Chapman, O. D. Gas Gangrene. Morbidity and Mortality in New York State, *New York State J. Med.* **38** 1015 (Jul. 15) 1938

therapeutic one before the operation,¹⁰ the trauma of the operation and especially a tight closure of the stump in poorly vascularized areas can readily activate the "resting" infection in the tissue spaces

Because of the remarkable results obtain by Kelly¹¹ in the treatment of gas gangrene with roentgen rays, we have also used prophylactic irradiation of the site of amputation in a few cases. The value of the procedure cannot be estimated from our limited material, as the incidence of gas gangrene following amputations in our series was not high, in a series observed at the Philadelphia General Hospital⁸ gas gangrene followed 67 per cent of amputations. When portable apparatus becomes generally available for prophylactic irradiation, more general use can be made of this method.

The second group of patients requiring amputation are not in immediate danger as to life. Their limbs are useless and intractably painful, their morale is shattered, and not infrequently they come to us loaded with opiates. If there is a little time to spare, one can try to break the drug addiction, at least in part, before the amputation, because the psychic shock of amputation together with sudden withdrawal of morphine or pantopon (a mixture of hydrochlorides of opium alkaloids) a few days after the operation produce a difficult situation. Sodium bromide both before and after the operation has seemed helpful. We would warn against the use of scopolamine for elderly patients as a preoperative medication, it seems that patients with cerebral arteriosclerosis or any other disturbance of cerebral circulation show a profound response to scopolamine. They may be difficult to arouse for twelve to twenty-four hours after injection of $\frac{1}{200}$ grain (0.3 mg.) of scopolamine, which is obviously undesirable. For patients under spinal anesthesia, $1\frac{1}{2}$ grains (96 mg.) of pentobarbital sodium is sufficient, for patients under general anesthesia, a small dose of morphine with $\frac{1}{150}$ grain (0.4 mg.) of atropine.

The preparation of the field needs some comment. Errors are frequently made in too extensive or too neglectful cleansing of the skin. The part to be removed should be carefully wrapped in cotton and gauze bandage and the edges bordering the surgical field glued to the skin with a 40 per cent solution of mastic in benzene. A soap and water preparation the night before and a gentle swabbing with alcohol in the operating room are sufficient. Iodine, especially in devascularized areas, does more harm than good. In amputations at the level of the midcalf or of the thigh the use of iodine is less objectionable.

¹⁰ This suggestion has been recently made by Callander and his associates (*Am J Surg* 42:811, 1938).

¹¹ Kelly, J. F. The Present Status of the X-Ray as an Aid in the Treatment of Gas Gangrene, *Radiology* 26:41 (Jan.) 1936.

but does not seem essential. A 2 per cent solution of brilliant green (a basic dye, the sulfate of tetraethyldiaminotriphenylmethane) may be conveniently used to outline the flaps.

ANESTHESIA

In our experience, spinal anesthesia is the method of choice for major amputations of the lower extremities, even midtarsal or toe amputations may be done well with small doses of a spinal anesthetic. For the spinal anesthetic from 100 to 120 mg of crystalline procaine hydrochloride dissolved in 2 to 3 cc of the patient's spinal fluid is used, the blood pressure is maintained with 0.5 cc of a 1 per cent solution of neo-synephrine hydrochloride, this is given just before the lumbar puncture, and the dose may be repeated when the blood pressure falls below the preoperative level.¹² The anesthesia so induced disturbs the patient's chemical equilibrium the least, diabetic patients may be fed by mouth a few hours after the operation. It has been our cus-

TABLE 1—*Methods of Anesthesia in Amputations for Peripheral Vascular Disease*

Type of Amputation	Anesthesia			Total Number of Cases
	Spinal	General	Intravenous	
Major	35	10	2	50
Minor	2	3	7	12

tom to insist on this type of anesthesia except in the following instances: (1) when the patient absolutely refuses spinal anesthesia, (2) when the patient is septic or comatose, in which case a very rapid amputation is done with the use of a small amount of ethylene, and (3) when the operation is so short that a small intravenous dose of pentothal sodium (sodium ethyl [1-methylbutyl] thiobarbiturate) suffices. Table 1 gives these data in detail.

METHODS OF AMPUTATION

With the exception of a few amputations of the upper extremities, which we are not reporting here, four types of amputation have been done in cases of peripheral vascular disease, namely, metatarsal amputation, amputation of the lower part of the leg, transcondylar amputation and supracondylar amputation. "High thigh" amputation was necessary in a few cases of embolic obstruction of the common iliac artery.

Metatarsal Amputation—Great credit is due to McKittrick,¹³ who in repeated publications has emphasized the important distinction between

¹² Brunner, R., and de Takats, G. The Use of Neosynephrine in Spinal Anesthesia, *Surg, Gynec & Obst* 68 1021 (June) 1939.

¹³ McKittrick, L. S. Indications for Amputation in Progressive Arterial Obliteration of the Lower Extremities. *Ann Surg* 102 342 (Sept) 1935.

infectious and circulatory gangrene. This is especially significant in cases of diabetes. A toe may be gangrenous because of an infected callus propagating infection toward the bone, with production of osteomyelitis, which in turn produces edema, thrombosis of digital vessels and the appearance of a sloughing defect. In such cases the pedal pulses may be impalpable, but the metatarsal region is warm, in fact, there is evidence of inflammation (rubor and pus formation). The reaction to histamine on the dorsum of the foot is positive. The patients, having been immobilized in bed for several weeks, resting on their heels, have deep abscesses under the plantar fascia, which may

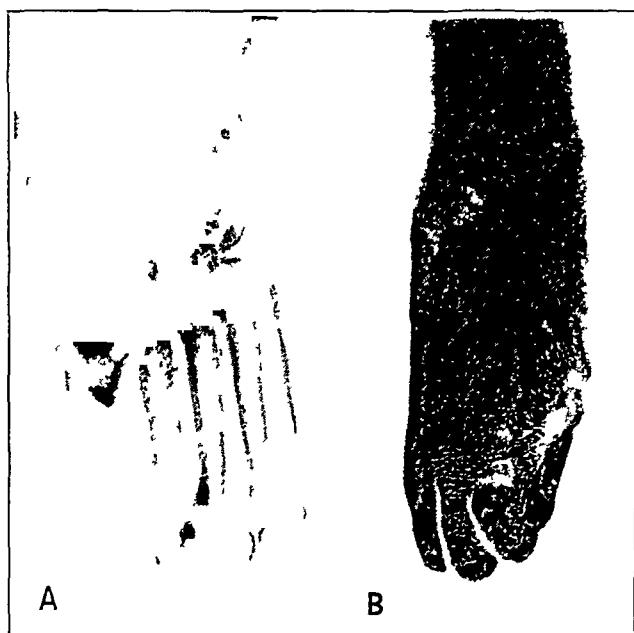


Fig 1—*A*, roentgenogram of the right foot of Eliza C, a 65 year old Negress. Note the subluxation of the third toe, which was not disturbed and did not interfere with walking. *B*, right foot of the same patient. The scar lies anterolaterally and is not painful. The patient walks on this foot without any discomfort or orthopedic appliance.

be easily overlooked and which may finally lead to loss of the foot. Even elderly diabetic patients tolerate the removal of one or more toes and make a good functional recovery if these abscesses under the plantar fascia are looked for and adequately drained. In the case of E. C., a 65 year old Negress, a metatarsal amputation of the first and second toes was performed. In order to get satisfactory anteroposterior drainage, the first metatarsal bone had to be amputated at a fairly high level (fig 1 *A*). After a long convalescence the foot healed

well, and the patient has been repeatedly examined, the last time being two years after the operation. She wears a metatarsal pad in her shoe (fig 1 B).

In cases of Buerger's disease it is usually wise to wait for demarcation of a gangrenous phalanx, when the whole digit is involved, causing intractable pain and threatening ascending infection, metatarsal amputation shortens functional and economic inefficiency. The flaps in such cases must be loosely sutured with a few interrupted sutures, without tension or drainage. In 2 recent cases a lumbar sympathectomy was performed prior to such an amputation, it markedly improved the collateral circulation at the level of amputation, increasing the chances of healing (fig 2).

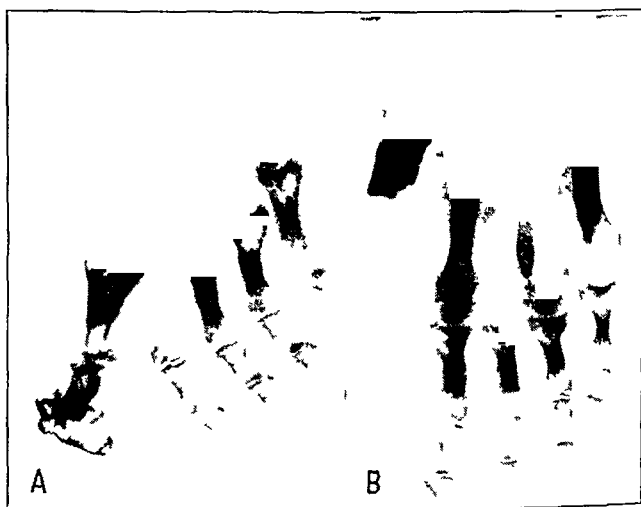


Fig 2—*A*, roentgenogram of the foot of Earl S, a 35 year old patient suffering from Buerger's disease. *B*, same foot after amputation. The wound healed slowly four weeks after amputation. Lumbar sympathectomy preceded the amputation.

For embolic gangrene of the toes a metatarsal amputation may be attempted, provided that a fair collateral circulation has developed down to that level. If the gangrene is dry and shows no signs of infection, from fifty to one hundred hours of intermittent venous hyperemia¹⁴ may help to develop the collateral circulation. Unfortunately, the feet in such a case are useless because of ischemic nerve paralysis or tendon contractures, so that a minor amputation can seldom be carried out.

¹⁴ de Takats, G., Hick, F. K., and Coulter, J. S. Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, *J. A. M. A.* 108: 1951 (June 5) 1937.

The worst chances for a successful minor amputation are found in cases of arteriosclerosis. This is in accordance with McKittrick's statistics¹³. It means that once amputation has been decided on, the metatarsal level is usually too low, even if the wound slowly heals, the stump is painful and cold and the foot useless for locomotion. Barring an exceptional case, this amputation is not apt to succeed and will have to be followed by a high amputation.

"Lower Leg" Amputation—Amputation of the lower part of the leg has obvious advantages over amputation through or above the knee. The associated mortality is lower, and preservation of the knee allows far better locomotion than is possible if the knee has to be sacrificed. It is far more difficult, however, to construct a satisfactory stump for patients suffering from peripheral vascular disease. An adequate muscular and fascial covering for the tibia, even when its crest is well chiseled off, is desirable, on the other hand, suture of the fascial planes in amputation for peripheral vascular disease increases the percentage of infection and mortality, as has been brought out by Taylor¹⁵. The ingenious method of Smith⁶ does away with a number of objections to amputations below the knee. He¹⁶ has recently reported on twenty such amputations for diabetic gangrene, with a mortality of 18.1 per cent. In a recent personal communication he reported 41 such amputations, with a mortality of 11 per cent, 95 per cent of the patients could wear an artificial limb. These results are so striking that an attempt should be made to reproduce them elsewhere. Our experience with this type of amputation is so small that it cannot be used for statistical purposes. Of the 3 patients in whose cases it was tried, 2 (with diabetes) died, probably owing to the increased trauma and the more difficult conditions of drainage following the operation. Recently, however, 5 such amputations were performed without mortality and with excellent functional results. For the material that we are dealing with, amputation of the lower part of the leg cannot often be considered. The patients either come to us with an ascending infection originating from preexisting gangrene or with such poor collateral circulation that an amputation below the knee cannot be successfully performed. For this reason we have become more and more convinced of the value of the transcondylar amputation of Callander.

Callander's Amputation—Most authors dealing with arteriosclerotic patients with or without diabetes agree that when amputation of toes

15 Taylor, F. W. Amputation Stump of Arteriosclerotic Gangrene, Surg., Gynec. & Obst. **67** 114 (July) 1938.

16 Smith, B. C. The Therapy of Surgical Complications of Diabetes Mellitus at Presbyterian Hospital in New York City 1930-1935. Surgery **2** 509 (Oct.) 1937.

is impossible the level of circulatory efficiency is at the knee. Among the many cases in which we have used histamine flares since 1930 there were only a few instances in which the flares were normal below the knee. Before the introduction of Callander's method¹⁷ amputation in such cases was done at the lower third of the thigh by the circular, or flap, method. Of 21 patients so treated, 7 died, a mortality of 33.3 per cent. In a comparable group of 26 patients amputation was done by Callander's method, with death of only 2 patients (7.6 per cent). These figures, however, hardly express the superiority of the method because of the weight-bearing ability of the stump, the lack of infection of the stump and the absence of need for secondary amputations.

Although the method has been twice described by Callander, its general use, as far as we can tell, is still delayed. Because it has given such satisfactory results in our hands, we wish to draw attention to it again. The method has not been modified, although a few insignificant points have been added to it.

Figure 3 shows the outline of the flaps, which we prefer to mark with a 2 per cent aqueous solution of brilliant green. These lines are shown as originally described by Callander, the posterior flap extending more distally than the anterior. In the 3 instances of marginal necrosis that were encountered the condition occurred on the posterior flap. This flap extends so far down and its viability can be so easily injured that it seems wise to make the two flaps extend distally to the same level, namely, to the tuberosity of the tibia.

In figure 4A the four internal hamstring muscles have been cut and are seen to retract. This, together with the severing of the adductor magnus muscle close to its femoral insertion, opens up the popliteal space, which can be approached at this point in the operation or, preferably, when the lateral wall of this space has been entered.

In figure 4B the popliteal space has been entered from the lateral side after the cutting of the tendon of the biceps femoris muscle and the iliotibial tract. The nerve is cut and sealed with electric cautery, and alcohol is not injected into it. This, we believe, diminishes the incidence of phantom limb pain and the incidence of neuromas. The use of the cautery was described by Hedri¹⁸ many years ago, and we have used it for several years. The artery and vein are tied separately with silk and transfixed with a silk suture, if they are closely matted together, as they often are, they may be tied and transfixed en masse.

17 Callander, C. L. A New Amputation in the Lower Third of the Thigh, *J. A. M. A.* **105** 1746 (Nov. 30) 1935, "Tendoplastic" Amputation Through the Femur at the Knee. Further Studies, *ibid.* **110** 113 (Jan. 8) 1938.

18 Hedri, A. Ein einfaches Verfahren zur Verhütung der Trennungsneurome, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **45** 50 1921.

Next, the knee joint is entered through the anterior flap (fig 4C) The patella is excised by sharp dissection, care being exerted not to injure the patellar ligament, which is later used to cover the sawed end of the femur No attempt is made to remove the synovial membrane, as it does not seem to interfere with prompt healing The posterior flap is then prepared, and the femur is freed just above the condyles, at a level shown in figure 3, which is lower than in the usual supracondylar amputations This results in a wider and heavier weight-bearing surface The bone is sawed off after a subperiosteal cuff is formed The bone marrow is not disturbed

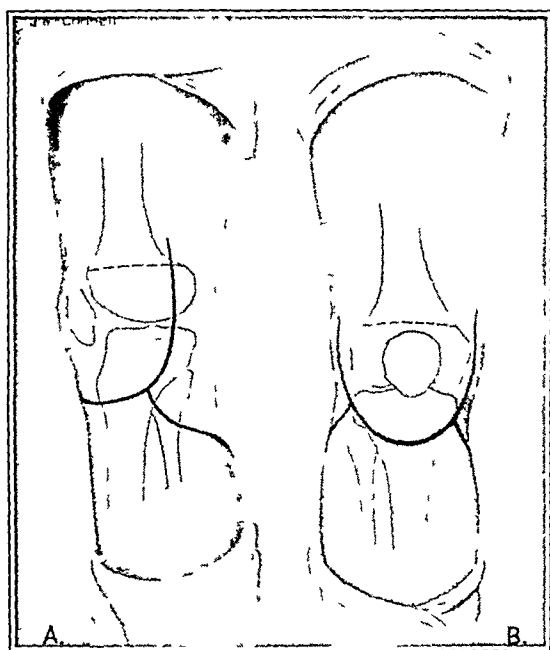


Fig 3—Outline of skin flaps for the amputation described by Callander A, lateral view, B, anteroposterior view The anterior flap is started about 4 fingerbreadths proximal to the internal condyle of the femur, at the well palpable border of the quadriceps femoris muscle It swings around through the level of the tibial tuberosity to the lateral border of the quadriceps muscle, ending at the same height as on the medial side Note that the posterior flap originates at right angles from the anterior flaps and reaches farther distally This may be the reason, together with a possible operative injury to the collateral arteries of the knee, for the occasional marginal sloughing of the posterior flap

Figure 4D illustrates the loose approximation of the two flaps by a few skin clips No suture has been placed into tendons or ligaments Copious drainage occurs for a few days after this amputation A drain may be placed under the posterior flap for a day or two It must not endanger the viability of the posterior flap Although the flaps look far

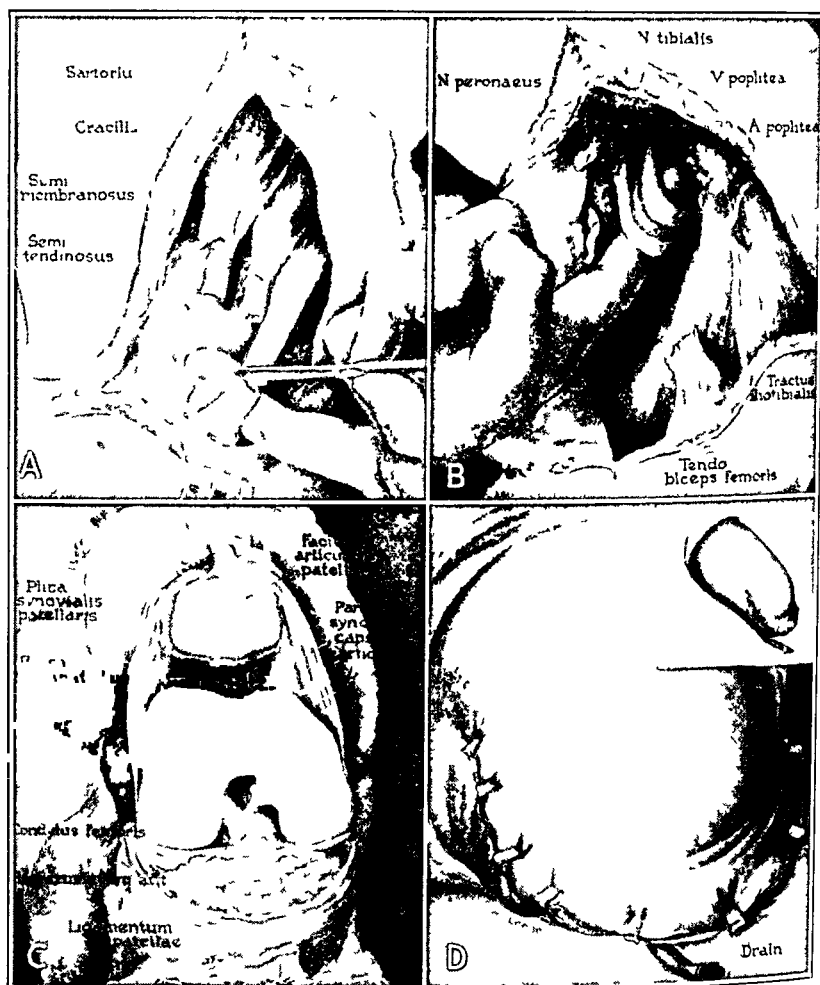


Fig 4—A, deepening of the incision of the anterior flap. The four internal hamstring muscles have been picked up and cut close to their insertion. They readily retract from the wound. Not shown here is the insertion of the adductor magnus muscle on the femur, which is also severed. B, exposure of the popliteal fossa from the lateral side. The tendon of the biceps femoris muscle and the iliotibial tract have been cut. The sciatic nerve or its two divisions are severed with the electric cauter. The vessels are tied with silk and transfixed to prevent slipping. C, exposure of the knee joint through the anterior flap. The patellar ligament is carefully saved, but the patella is discarded. The femur is sawed off just above the cartilage, and the patellar fossa is fitted into the sawed surface. D, final stage of the operation. The two flaps are allowed to fall together. No sutures are placed in the patellar ligament. Only a few skin clips are placed to approximate the edges of the skin. If there is a large dead space under the posterior flap, this may be drained for twenty-four hours. Copious drainage occurs between the skin clips, when this subsides, in four to five days, more clips are applied for accurate closure of the wound. The flaps, which at first seem far too long, rapidly retract.

too loose for a few days, an astonishing amount of retraction takes place in the posterior flap, so that the suture line is far enough from the weight-bearing surface (fig 5)

MORTALITY STATISTICS

Excluding amputations of toes and metatarsal amputations, which were followed by no deaths, we are presenting our data on 50 major amputations. Of the 50 patients, 14 died, a total mortality of 28 per cent (tables 2 and 3). This is lower than the figures from the Philadelphia General Hospital⁵ and those from the Cook County Hospital

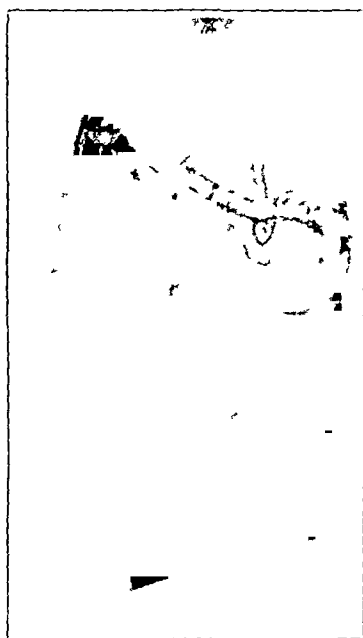


Fig 5—Amputation stump ten days after a Callander amputation. Ten days later a temporary peg leg was applied. The mobility of the flaps and the painless, direct weight-bearing stump always astonishes the makers of the artificial limb.

in Chicago¹⁹ but much higher than the figures of McKittrick¹³ and those of Smith¹⁶. Although the number is too small to warrant statistical analysis of such factors as age, infection, absence or presence of diabetes and absence or presence of arteriosclerosis, it is obvious that advanced age, diabetes and extensive cardiac damage, but especially generalizing sepsis, raise the mortality rate. We were interested, however, in dividing these cases according to the type of amputation performed (table 4). At present we have not enough experience with the

19 Apfelbach, G. L. The Surgical Management of Lesions Peculiar to Diabetes Mellitus, Illinois M J 56 332 (Nov.) 1929

technically delicate amputation of Smith to express any opinion on it but the difference in results between the customary "low thigh" amputation and the Callander amputation is striking. The mortality rate dropped from 33 per cent to 7.6 per cent, although the selection of cases, the material and the surgical personnel were the same during the five year period. The Callander amputation provides for copious drainage for the first few days without sacrificing stump length and also with

TABLE 2—*Causes of Death Following Amputation for Peripheral Vascular Disease*

	Number of Deaths
Bronchopneumonia	2
Coronary occlusion	2
Delayed shock	1
Cardiac failure	1
Sepsis	8
Total	14

TABLE 3—*Types of Gangrene Necessitating Major Amputation**

Gangrene	Number of Cases	Number of Deaths
Diabetic	30	10
Arteriosclerotic	11	2
Postembolic	6	2
Post thrombotic	3	0
Total	50	14

* In no case of Buerger's disease was amputation performed above the metatarsal level

TABLE 4—*Mortality Following Various Types of Amputation*

Type of Amputation	Number of Cases	Percentage of Deaths
Metatarsal	15	0
Lower third of thigh	21	33
Callander	26	7.6
Total	62	14.5

out prolonging the stay in the hospital, as secondary closure is easily accomplished. A comparison of the period of hospitalization with the two amputations shows that after twenty-one amputations at the lower part of the thigh the average number of days in the hospital was twenty, as compared with a stay of eleven days after twenty-six Callander amputations. Some patients were discharged as early as six days after the operation.

EMERGENCY AMPUTATIONS

When patients are first seen in a septic, dehydrated, sometimes comatose or delirious, state, little time should be lost in performing an emergency amputation. We have been repeatedly amazed at the effect

of such an amputation on a comatose, moribund patient. Obviously the mortality rate of such amputations is higher, the mortality rate of our deliberate amputations was 14.5 per cent, while that of 15 emergency amputations was 33 per cent. We feel, however, that in the last year we have decreased this mortality by (1) doing a rapid guillotine amputation below or above the knee in eight to ten minutes, (2) using morphine-scopolamine premedication and a slight quantity of nitrous oxide with plenty of oxygen for the anesthetic, (3) giving transfusions, sulfanilamide and anti-gas gangrene serum before and after the operation, and (4) leaving the stump wide open, without a single suture, and using dependent drainage instead of the frequently employed elevation of the stump.

It is difficult to foresee when a gangrenous leg will become suddenly a source of general septicemia and toxemia. The patient may be admitted to the hospital in good general condition, with a slight fever in the evening or none at all and with moderate leukocytosis. Within a day or two the patient may suddenly become septic, and one has a feeling that valuable time has been lost. Although preparation with anti-gas gangrene serum and diabetic control are, of course, desirable, no time should be lost if septicemia is threatening or is present. The best treatment for the patient's diabetes is to get rid of the source of infection, and only the acidosis needs to be controlled.

REAMPUTATIONS

Stumps may have to be reamputated because of tight skin, spurs, neuromas or marginal necroses of bone, but in cases of vascular disease a problem arises regarding the secondary closure of guillotine amputations. Guillotine amputations through the lower part of the leg or the thigh have occasionally been done on septic, comatose patients under gas anesthesia of short duration, it is remarkable how these severely handicapped patients tolerate such a rapid amputation. It is customary, however, from two to three weeks after this operation to resect the protruding bone and close the skin over it. Such operations frequently result in a flare-up of the latent infection, which necessitates reopening of the stump and results in further delay in healing. Of 8 cases of guillotine amputations in which the stump was subjected to secondary closure, a marked flare-up occurred in 4, 1 patient, seen in consultation in another service, had general septicemia. We have come to the conclusion that skin flaps should be prepared at the first operation. Should the shrinkage be so extensive that secondary closure is impossible it is better to use skin grafts to cover the stump than to reamputate through a previously infected field. Another method used was to do a Callander amputation after a guillotine amputation through the lower part of the leg. By this method the infected field is not reentered.

THE ARTIFICIAL LIMB

If primary union takes place, a temporary peg leg is constructed and worn by the patient within four to six weeks. Patients above the age of 65 years, with some notable exceptions, hardly ever learn the use of an artificial leg. In table 5 we give the number of patients who have received and used a prosthesis after amputation. Again the superiority of the Callander type of amputation is evident, although, as Smith¹⁶ has repeatedly pointed out, patients whose legs have been amputated below the knee by his modified guillotine technic have worn prostheses in about 95 per cent of cases, about 90 per cent of his patients whose legs have been amputated at the thigh could not or would not wear a prosthesis, but the amputations were not done with the Callander technic.

The cause of refusal to wear an artificial limb, excluding senility, other incapacitating illnesses and financial difficulty, lies mostly in the

TABLE 5—*Use of Artificial Limb*

Type of Amputation	Number of Patients Traced	Wearing Limb
Lower part of leg	3	2
Lower third of thigh	14	8
Callander	20	16
Total	37	26

stump itself or in the indifference of the surgeon toward urging functional rehabilitation. Finally, there is the condition of the other limb

FATE OF THE OTHER LIMB

Except when there is embolic occlusion in one limb, it is a general rule that the limb remaining after amputation suffers from impairment of circulation, although frequently in a much less advanced form. With the help of pulses, oscillometric curves, histamine flares and sudden changes in cutaneous temperature, one should be oriented as to the stage of vascular impairment. That the heel and all bony prominences should be protected while the patient is bedridden is obvious. We have made routine use of intermittent venous hyperemia¹⁴ before and after amputation of the other limb. Nevertheless, because of the strain on the single leg, we have seen a number of patients return with a rapid exacerbation of the vascular status of the remaining leg. For this reason the status of the remaining leg must be thoroughly considered before the use of an artificial limb is urged. Actually, of the 50 cases in this series the other limb was later amputated in only 3, but this does not indicate the percentage of limbs which subsequently become gangrenous.

COMMENT

Such a mutilating operation as amputation is unwelcome to both patients and surgeons. It is unavoidable, however, in case of sudden arterial occlusion that could not be or was not subjected to embolectomy or of chronic vascular occlusion for which effective conservative treatment was not started in the early stages. A diagnosis of "rheumatic pains" or "flatfoot" is still made too often in the early stages of peripheral vascular disease, and much valuable time is lost by ineffective or harmful measures. A combination of sympathectomy and amputation of toes might also save from major amputations a number of patients suffering from advanced forms of Buerger's disease.



Fig 6—Massive gangrene of the right leg. Miss M. H., 80 years old, mildly diabetic, had a small gangrenous patch over a bunion. The gangrene rapidly spread, producing profound toxemia. With adequate diabetic control and fluid intake she was kept alive for several weeks. She died of acute coronary occlusion. Amputation was not attempted. (Case of Dr. George H. Coleman.)

Few patients are so independent financially that rest in bed for months in a favorable climate with adequate nursing care is feasible. The urgency of restoring the patient's earning capacity should always be kept in mind. Massive gangrene calls for prompt amputation except in cases of extreme senility (fig 6), as a well localized dry gangrene may develop overnight into rapidly progressive toxemia and septicemia, with an increased rate of mortality and need for prolonged hospitalization. Although the utmost conservatism must be observed in advocating the loss of any part of the extremities, no time should be lost in removing a part which is obviously lost and which no magic can recover.

For several years we have kept records (1) of patients who were urged to have an amputation but refused when first seen and (2) of the financial strain which the patient has shouldered before he submitted to amputation. Of the 10 patients who were urged to have a major amputation and refused, 3 returned within six months to us, 4 had an amputation elsewhere and 3 could not be traced. Among 15 patients on whom data in regard to medical expenses are available, three groups were established. Five patients who were unemployed or earned less than \$100 a month were on relief from two to four years because of inability to work, 3 of these were rehabilitated and regained their earning power. Seven patients whose income was from \$150 to \$300 a month had spent from \$1,500 to \$3,500 (approximately one year's income) for medical care and were devoid of reserves when they came to amputation. Three patients in the upper brackets of income had spent an average of \$5,000 to save an obviously lost extremity.

We wish to make it clear that we do not refer to patients who with conservative therapy (in which we include sympathectomies and amputation of digits) have a fair chance to retain the limb. The crux of the situation lies in defining this "fair chance to save the limb," as in the other two groups, namely, patients with good collateral circulation and patients with massive gangrene and increasing toxicity, the indications are well defined and need no elucidation.

SUMMARY

The indications for amputation and the methods and results of amputations done in certain cases of peripheral vascular disease have been discussed. Determination of the proper level of amputation and preparation of the patient are described. Factors decreasing mortality are emphasized. The study was based on 50 major amputations. Although a mutilating operation, amputation for vascular disease continues to rehabilitate economically handicapped or seriously endangered patients for whom conservative measures are ineffective. The mortality can be reduced to a small, unavoidable percentage, especially by amputating before infection is superimposed on gangrene.

PERIARTERITIS NODOSA SIMULATING AN ACUTE ABDOMINAL CONDITION REQUIRING OPERATION

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Periarteritis nodosa was first accurately described by Kussmaul and Maier¹ in 1866. Since that time, many detailed case reports have appeared in journals devoted to pathology or to internal medicine. The frequency with which this disease simulates acute conditions requiring surgical treatment justifies its emphasis in the surgical literature.

Periarteritis nodosa or, better, polyarteritis nodosa, is primarily a disease process involving the walls of blood vessels. The lesions start with edema and subsequent necrosis in the media of the vessel wall. The process ultimately extends to the intima, with reactive cellular proliferation which frequently produces endothelial injury and thrombus formation. There is also an adventitial infiltration of polymorphonuclear leukocytes, often accompanied by eosinophils. The healing process with the laying down of connective tissue results in the formation of a nodule involving the vessel wall, lack of repair, mural degeneration and necrosis with destruction of elastic fibers may terminate in aneurysm formation. Nodule formation may also be due to a prominent cellular infiltrate without fibrous tissue proliferation, as was seen in a number of the involved vessels in the case reported here. There is often observed in the vicinity of the cellular infiltrate and necrosis a fibroblastic proliferative intimal response. These lesions have a distinct predilection for the arterial side of the circulation, although involvement of venous walls has occasionally been observed. The medium-sized and smaller arteries are predominantly the site of the lesions. In the cases reported in the literature, the vessels of the lungs, central nervous system and bones seem to be infrequently affected, while the renal arteries are almost invariably involved.

REPORT OF A CASE

W. W., a small white man, was admitted to the medical service of the Knickerbocker Hospital on April 29, 1939. The past history was irrelevant except for gonorrheal urethritis in 1932. This had been treated and cured. The present

1 Kussmaul, A., and Maier, R. Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsches Arch f klin Med* 1 484, 1866.

illness started six weeks prior to the patient's admission to the hospital, when there was a sudden onset of severe pain in the back. This was followed in a few days by cloudiness of the urine. Within two days the pain radiated into both flanks and the upper part of the abdomen, and a few days later it progressed to the lower part of the abdomen and into the testicles. The patient was constipated at that time and took castor oil, after which there was a very dark stool. He visited the outpatient department of another hospital and was told he had an ulcer of the stomach, although no roentgen or laboratory studies were made. Medicine was prescribed, and immediately after taking it he began to vomit. Three weeks before admission he stated that the pain had left the lower part of the abdomen and localized in the right upper quadrant. He then began to have daily chills, after which he felt feverish. He continued to vomit frequently and lost 30 pounds (13.6 Kg) in the six weeks prior to admission. An increase in severity of the pain in the right upper quadrant caused him to seek care in the hospital.

The patient appeared chronically and acutely ill. The positive findings were limited to the abdomen and back. There was tenderness throughout the abdomen, most marked in the right upper quadrant, and in this area there were muscle spasm and rebound tenderness. There was tenderness in both costovertebral angles, more marked on the right side. Tenderness on pressure was elicited over the lower border of the liver, which was about 1 inch (2.5 cm) below the costal margin. The knee jerks were exaggerated, and the lower abdominal reflexes could not be obtained. The temperature was 101 F on admission and ranged irregularly between 100 and 102 F. The blood pressure in millimeters of mercury was 102 systolic and 78 diastolic. The pulse rate was 90 per minute. The erythrocyte count was 3,850,000 per cubic millimeter of blood, with 76 per cent hemoglobin. The leukocyte count was 18,000 per cubic millimeter, with 96 per cent polymorphonuclear leukocytes. The Wassermann reaction of the blood was negative. The value for nonprotein nitrogen was 27 mg per hundred cubic centimeter. Repeated urinalyses revealed no abnormality. The benzidine reaction for blood in the stool was 4 plus. Five days later this reaction was negative.

The patient was seen by members of the medical and surgical staff, and the diagnoses considered included right perinephric abscess, appendical abscess and cholecystitis. Forty-eight hours after admission, the rigidity of the right upper quadrant became boardlike, and one of the surgeons felt that he was dealing with a penetrating peptic ulcer. During the next week the rigidity of the right upper quadrant persisted, and nine days after admission the abdomen was explored. At operation numerous adhesions were found between the omentum and the anterior abdominal wall. There were a normal-appearing appendix and a markedly thickened gallbladder about one and a half times the normal size, surrounded by a few adhesions. The stomach appeared normal. A cholecystectomy and an appendectomy were performed, and material for biopsy was removed from the liver. The true diagnosis was made on microscopic examination of the specimens, the lesions being found in the arteries of the gallbladder, appendix and liver (figs 1 and 2). The arterial walls showed cellular infiltration of fibroblasts, reticulum cells and a few polymorphonuclear leukocytes. No eosinophils were seen. This infiltration involved the entire wall of the artery and extended into the perivascular tissue. Some vessels showed areas of fibrous replacement of their various layers. No aneurysms were encountered. The vascular lesions of the liver were within the portal fields and were confined chiefly to the arteries. In this viscus the periadventitial infiltration frequently exceeded that within the

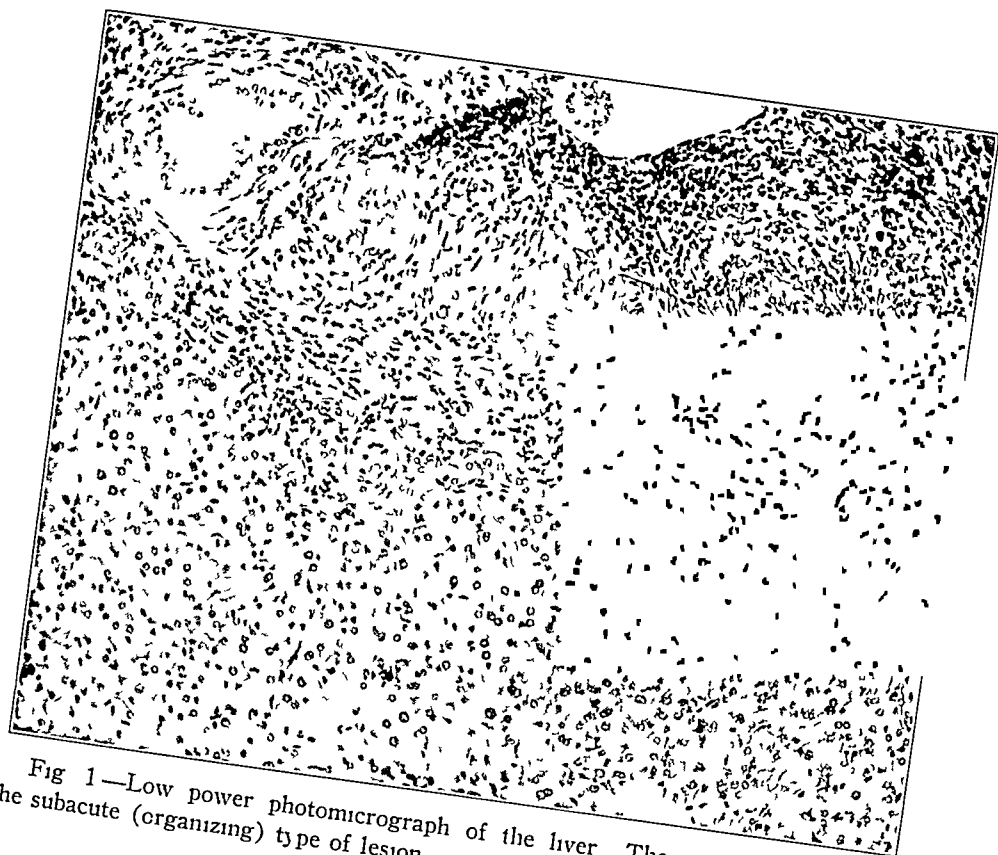


Fig 1—Low power photomicrograph of the liver. The arterial wall shows the subacute (organizing) type of lesion.

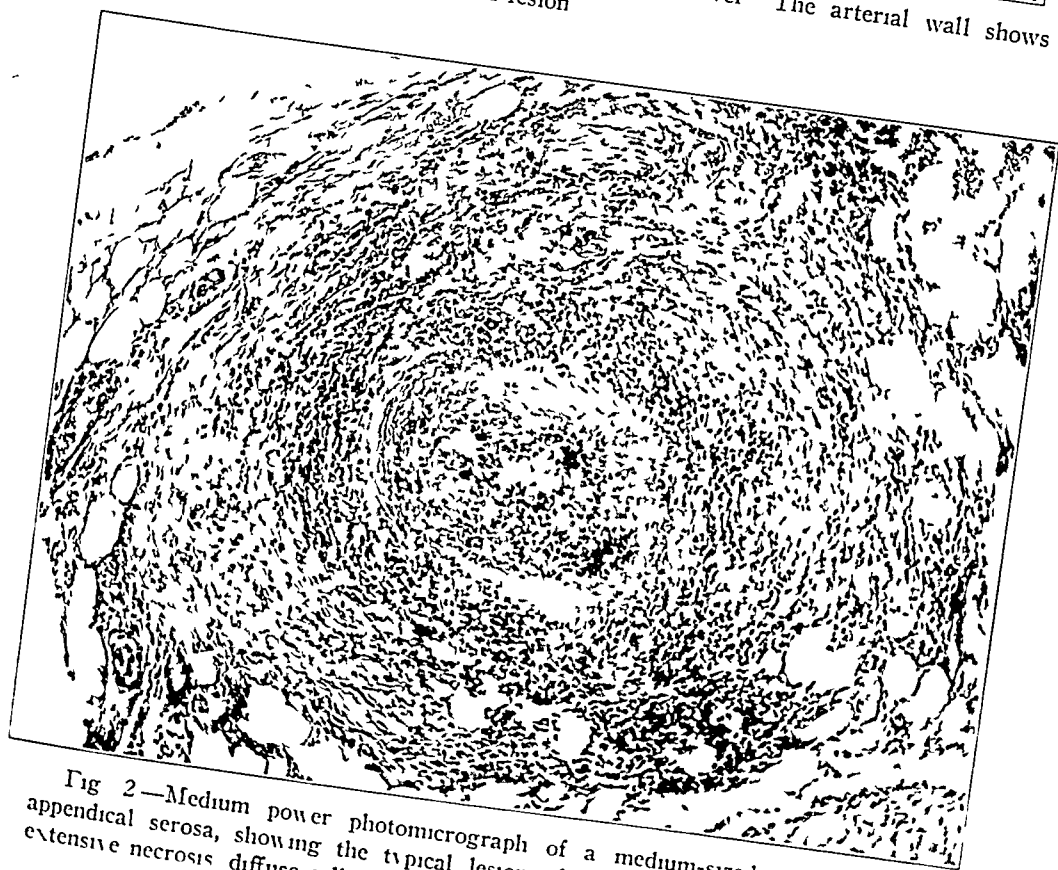


Fig 2—Medium power photomicrograph of a medium-sized artery in the appendiceal serosa, showing the typical lesion of periarteritis nodosa. Note the extensive necrosis, diffuse cellular infiltration, and thrombus formation.

vessel wall. In one area of the liver an adjacent venule in the portal field was found to be involved. Evidence of subacute perihepatitis was noted. The wall of the gallbladder showed evidence of reactive acute and chronic inflammation, evidently the sequel of the vascular lesions. Postoperatively, the patient made a remarkably uneventful convalescence. In spite of transfusions the erythrocyte count and the hemoglobin concentration remained low, and the leukocyte count averaged about 12,000 per cubic millimeter, with 80 per cent polymorphonuclear leukocytes. Numerous differential studies of the blood smears revealed from 2 to 6 per cent eosinophils. Repeated chemical studies of the blood showed

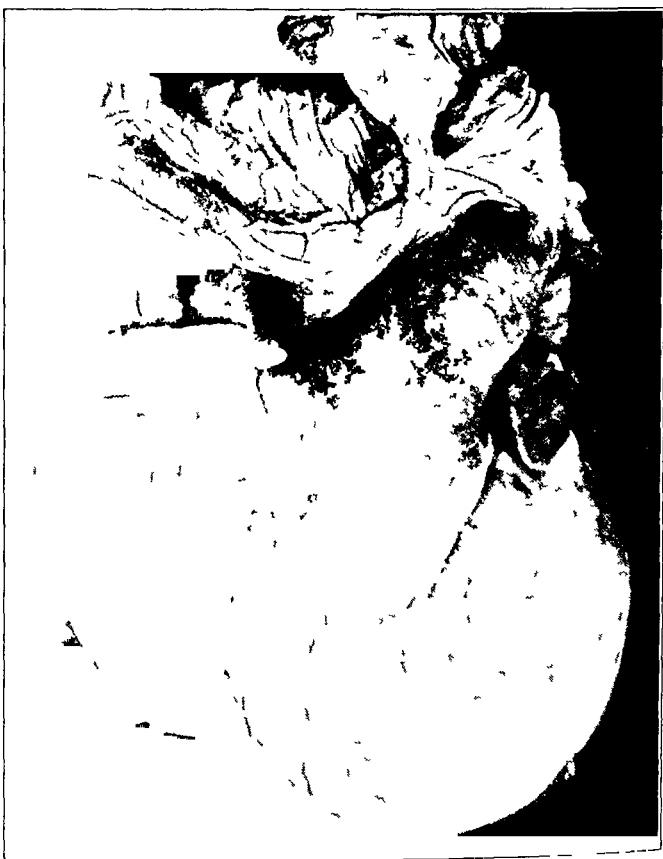


Fig 3—Heart. Note the increased prominence and nodular thickening of the branches of the coronary arteries, the pericardial scars and the multiple pericardial hemorrhages. The central zone of pericardial thickening indicates the site of a myocardial infarct.

values within the normal range for nonprotein nitrogen, uric acid and creatinine. The patient was discharged to a convalescent home on May 28.

He was readmitted to the hospital on August 2. At this time he presented a picture of chlorotic marasmus, a most descriptive term used by Kussmaul and Maier¹ to describe this condition. He was emaciated, had a pinched facies, was sallow with an icteric tinge and was markedly dehydrated. Morphine in large amounts was required to control the pain in his back and abdomen. Laboratory examination at this time revealed pronounced secondary anemia, a value for

nonprotein nitrogen of 98 and an icteric index of 61. The urine gave a 3 plus reaction for albumin. It contained a few hyaline casts, many white blood cells and a few red blood cells. The blood pressure rose to 154 systolic and 110 diastolic. The jaundice rapidly increased, and bilateral parotitis developed. He died on October 10, seven months after the onset of symptoms.

At necropsy there were observed multiple infarcts of the kidneys and liver. There were recent and old ulcers of the gastrointestinal tract, the jejunum presenting a penetrating ulcer with localized acute fibrinous peritonitis. The large intestine disclosed an acute and subacute hemorrhagic type of ulcerative colitis incident to the vascular abnormalities. The heart was hypertrophied and dilated and presented many recent as well as old myocardial infarcts, a recent infarct of the wall of the right auricle, acute diffuse hemorrhagic pericarditis and mural thrombosis of the left auricular and ventricular chambers. There were multiple recent emboli in the branches of the pulmonary arteries, with infarction of the parenchyma of the lung. The adrenal glands and testicles presented evidence of recent hemorrhage. The characteristic lesions of *periarteritis nodosa* were demonstrated in the coronary, gastrointestinal, mesenteric, renal and hepatic arteries (fig. 3).

COMMENT

In the pre-Wassermann era this disease process was thought to be syphilitic in origin, most likely because of the tendency to aneurysm formation. Patients whose cases have been reported since that time, however, have shown no higher percentage of positive Wassermann reactions than have a similar group unaffected by this disease. Recent or prodromal infections the convalescence of which seems to merge with the onset of this disease have been reported in more than half the cases. In Spiegel's² report on 17 patients, 7 had prodromal infections immediately preceding the onset of symptoms, and 2 had had preceding atypical scarlet fever within two months. The hemolytic streptococcus is the organism most frequently associated with the prodromal infection. The disease has been known to occur at all ages from infancy to senescence. More than 50 per cent of the patients, however, are in the age group between 20 and 40. Males are more frequently affected, there were 4 males to 1 female in Gruber's³ series of 113 patients.

The disease is typically chronic and progressive, lasting a few weeks or at most a few months. The symptoms are amazingly variegated and fleeting, the first ones being referable to the system or viscera whose arteries are first affected. Frequently, one set of symptoms may improve or entirely subside as the lesions in the vessels heal and their lumens recanalize or as collateral circulation develops, only to be followed or overlapped by an entirely new symptom complex. In many cases an erroneous diagnosis of "surgical abdomen" is made. Seven of

2 Spiegel, R. Clinical Aspects of *Periarteritis Nodosa*. *Arch. Int. Med.* 58: 993 (Dec.) 1936.

3 Gruber, G. B. Zur Frage der *Periarteritis nodosa*. *Virchows Arch. i. path. Anat.* 258: 441, 1925.

Spiegel's ² patients were treated with celiotomy, the diagnosis of appendicitis having been made preoperatively in 5 instances. When the viscera of the upper part of the abdomen are involved, a diagnosis of cholecystitis or pancreatitis is often made. Singer ⁴ reported the cases of 2 patients, 1 of whom was subjected to cholecystectomy, while the other escaped the same operation because of unexplained delirium. Penetrating ulcers of the intestinal tract resulting from infarction of the wall of the intestine are common. The early and almost constant involvement of the renal arteries causes pain in the back radiating into the flanks and abdomen. This phenomenon is well demonstrated in the present case. Earlier reports indicated that this disease always resulted fatally, most likely because it was usually reported by the pathologists. The more recent literature indicates that in about 10 per cent of cases the patient may recover or the disease become arrested for long periods.

SUMMARY

A case is reported in which the patient was operated on for a penetrating peptic ulcer, the exploration revealing no evidence of ulcer but an apparently chronic cholecystitis. A cholecystectomy and an appendectomy were performed, and material for biopsy was removed from the liver. Pathologic examination of the specimens revealed the changes in the gallbladder to be due to a disease of the blood vessels supplying it, namely, periarteritis nodosa. The outstanding clinical and pathologic features of the disease are discussed. Emphasis is placed on the frequency with which periarteritis nodosa is incorrectly diagnosed as a lesion requiring surgical intervention.

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⁴ Singer, H. Periarteritis Nodosa, with Special Reference to the Acute Abdominal Manifestations. Report of Two Cases, *Arch Int Med* **39** 865 (June) 1927.

PERIPHERAL VASOSPASM FROM TOBACCO

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Tobacco, regardless of its form or the manner in which it is used, produces peripheral vasospasm

The earliest use of tobacco and toxicologically allied plants by man antedates written records. Its introduction to Europe was concomitant with Columbus' second voyage to America, and the ecclesiastic Fia Romano Pane is credited with the act. He was the first to describe the effects of smoking the plant. These, as he observed them, were a quieting influence, the production of pleasant dreams and the transport of the smoker to another world. He also recognized the variation in strength of different tobaccos.

Little was known concerning the principles responsible for the general effects of using tobacco until its chief alkaloid, nicotine, was isolated by Posselt and Reimann at Heidelberg, Germany, in 1828. This discovery may be considered the basis for most of the subsequent experimental work on tobacco, and the pharmacologic and toxicologic character of the plant is, for practical purposes, solely that of nicotine¹. The fact that the leaf is smoked, however, introduces the possibility that intermediary products of combustion are in part responsible for the physiologic changes associated with the act.

Tobacco smoke has been shown by Lee² and later by Dixon³ to contain as its main constituents nicotine, pyridine bases, carbon monoxide and ammonia, in addition, traces of cyanides and sulfocyanates are found. The substances readily absorbed by the body are nicotine and carbon monoxide, and they are therefore the only elements capable of producing general physiologic effects. The others are of interest solely

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Aided by a grant from the James and Elizabeth Inglis Fund for Surgery Research

1 Cushny, A. R. A Text-Book of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1936, p. 464. Sollmann, T. H. A Manual of Pharmacology, and Its Applications to Therapeutics and Toxicology, ed. 3, Philadelphia W. B. Saunders Company, 1926, p. 406.

2 Lee, E. Quart J Exper Physiol 1:35, 1908.

3 Dixon, W. E. Brit M J 2:719, 1927.

because of their local irritative propensities and are held responsible for the conjunctivitis, morning cough and irritation of the mouth and tongue frequently experienced by heavy smokers and by frequenters of smoke filled rooms

The amount of carbon monoxide in tobacco smoke in general varies directly with the diameter of the smoking surface and the moisture present. Baumberger⁴ stated that as cigaret smoke reaches the mouth it may contain as much as 7.2 to 25 parts of carbon monoxide in 10,000 parts of air. Theoretically, with continuous smoking of cigaretts for one hour at five puffs per minute, the blood of the smoker might be 22 per cent saturated with carbon monoxide. Practically, however, Ruhl and Lin⁵ found that the highest point of saturation of the blood actually reached in inhalers is between 1 and 2 volumes per cent, the average being but 0.52 volumes per cent. This degree of saturation cannot be of physiologic significance except at very high altitudes. Thus, any general physiologic effect that is consistently observed to be associated with the use of tobacco can, with only slight reservation, be ascribed to nicotine. The nicotine actually absorbed in smoking or chewing varies with the variety of tobacco used.⁶ The form in which the tobacco is smoked also determines the amount of nicotine available for absorption, the largest amounts per unit of weight being obtained from cigars and pipes and the smallest from cigaretts. This result is due to the more nearly complete combustion of the nicotine in the cigaret. Also, the drier the tobacco smoked, the better the combustion and the smaller the nicotine content of the smoke. Baumberger⁴ found that on an average 0.573 per cent of the cigaret by weight appears as nicotine in the smoke. Since the weight of a cigaret is approximately 1 Gm., about 3.878 mg. of the alkaloid is taken into the oronasal and respiratory passages, the amount actually absorbed, however, Baumberger concluded, is less, since absorption is not complete and only 66.7 per cent, or 2.52 mg., is assimilated by a noninhaler and 88.2 per cent, or 3.33 mg., by an inhaler. Maddock and Collier⁷ found that 1 mg. constitutes an adequate stimulus when administered intravenously to the human subject.

There can be little doubt, therefore, that the smoking of one cigaret provides an amount of nicotine sufficient to account for the vascular reactions to be ascribed to tobacco. Certain experimental controls will be described as proof positive of this contention.

4 Baumberger, J. P. *J. Pharmacol. & Exper. Therap.* **21** 23, 35 and 47, 1923.

5 Ruhl, A., and Lin, P. *Deutsche med. Wchnschr.* **62** 493, 1936.

6 Wright, I. S., and Moffat, D. *Effects of Tobacco on the Peripheral Vascular System. Further Studies*, *J. A. M. A.* **103** 318 (Aug. 4) 1934.

7 Maddock, W. G., and Collier, F. A. *Ann. Surg.* **98** 70, 1933.

Voluminous studies by many workers on the pharmacology of nicotine have shown that it is very complicated. The drug has three sites of action, namely, the central nervous system, all the ganglions of the autonomic nervous system (thoracolumbar and craniosacral) and the nerve ends of voluntary muscle, at which it produces primary stimulation followed by paralysis. The amount of the drug needed to produce the latter effect is large and is not obtained by smoking. The vascular reaction may be elicited by action of the drug on the vasomotor center as well as on the ganglions of the sympathetic and parasympathetic nervous systems. Vasomotor reactions to smoking may, in general, be considered the result of stimulation of the cells of the central and of the sympathetic nervous system. Euziere and his associates⁸ suggested an additional mechanism of action that of sensitization of sympathetic reflex mechanisms to adequate stimuli.

Actual experimental work on the effect of smoking on the peripheral vascular reactions of man was begun by Bruce and his associates⁹ in 1909, when they demonstrated the peripheral vasoconstrictor action of tobacco by means of the plethysmograph. Simici and Marcu¹⁰ and also Ralli and Oppenheimer¹¹ later carried out the same sort of studies. No publication, however, made reference to this important work in a consideration of the apparent relation of tobacco and thromboangitis obliterans until that of Maddock and Coller⁷ in 1933. Experimental work by them with cutaneous temperatures used to show the peripheral vasoconstrictor effect of tobacco, although it did not demonstrate any casual relation between tobacco and thromboangitis obliterans, firmly established the important therapeutic principle that no tobacco should be allowed persons with this disease. This principle had been previously laid down independently by Buerger,¹² Silbert¹³ and Samuels¹⁴ on the basis of clinical observations.

8 Euziere, J., Castagne, R., Lafon, R., and Benédittini, A. I. *Bull. Acad. de med., Paris* **116** 615, 1936.

9 Bruce, J. W., Miller, J., and Hooker, D. *Am. J. Physiol.* **24** 104 1909.

10 Simici, D., and Marcu, Q. *J. de physiol. et de path. gen.* **25** 57 1927.

11 Ralli, E. P., and Oppenheimer, B. S. *Proc. Soc. Exper. Biol. & Med.* **26** 9, 1928.

12 Buerger, L. *The Circulatory Disturbances of the Extremities*, Philadelphia W. B. Saunders Company, 1924.

13 Silbert, S. *Thrombo-Angitis Obliterans (Buerger). Results of Treatment with Repeated Injections of Hypertonic Salt Solution*. *J. A. M. A.* **94** 1730 (May 31) 1930.

14 Samuels, S. S. *Treatment of Gangrene Due to Thrombo-Angitis Obliterans*, *J. A. M. A.* **96** 751 (March 7) 1931.

The experimental findings of Maddock and Coller⁷ have since been substantiated and extended by Barker,¹⁵ Wright and Moffat⁶ and Lampson¹⁶ in the United States and by Euziere abroad

The experimental work reported in this paper was performed at the University of Michigan Hospital. The effect of smoking on the vascular system of normal subjects was first investigated. Environmental factors were well controlled, the room temperature being maintained between 25 and 28 C in order to make sure that peripheral vasospasm was not present to any great degree at the beginning of the experiment. An electric fan, running at low speed, provided a constant circulation of air. Psychic stimuli were eliminated as well as possible by insistence on quiet and recumbency of the subject for one hour prior to any observations.

Determinations of cutaneous temperature with the (Tycos dermatherm) of the palmar surfaces of the fingers and the plantar surfaces of the toes and pressure and pulse readings were made at intervals of five minutes throughout the experiment. Tobacco was withheld for a sufficient period to establish the fact that an essentially steady state existed. The subject was then given his usual form of tobacco to smoke in his usual manner. Observations were continued after completion of the act of smoking until definite recovery had ensued. Twenty subjects including both "light" and "heavy" smokers, were observed. In all cases a progressive decrease in cutaneous temperature of the extremities and an increase in blood pressure and pulse rate occurred shortly after the beginning of smoking and persisted after cessation. For some subjects oral and truncanl temperatures were recorded, these showed no change. The recovery period was of varying length in different instances, in none was it less than five or more than seventy minutes. Interestingly, it was found that the temperature of the fingers returned to normal more rapidly than did that of the toes, the difference being as much as three minutes in some cases. When a second cigaret was smoked after recovery, the changes just described occurred in parallel degree. Chart 1 illustrates graphically a typical result. The extent of the reaction and the time necessary for recording are apparent. No significant consistent variation in the responses of "heavy" and those of "light" smokers could be established.

It was recognized during these experiments that factors other than nicotine might have been responsible for the phenomena noted. The possibility that the altered rate, rhythm and depth of breathing incident to smoking might produce the changes was first investigated. The subject

15 Barker, N. W. Proc. Staff Meet., Mayo Clin. 6 65, 1931

16 Lampson, R. S. Quantitative Study of Vasoconstriction Induced by Smoking, J. A. M. A. 104 1963 (June 1) 1935

was given a small paper tube or an empty pipe and instructed to carry out smoking movements, simulating as nearly as possible actual smoking. Negligible changes in pulse rate, blood pressure and cutaneous temperature occurred. Mulinos and Shulman¹⁷ have since reported peripheral vasoconstriction in the hand associated with deep breathing but we feel that this played no role in the experiments cited here. The possibility that carbon monoxide or other products of incomplete combustion of organic matter might have played a part was ruled out when no vascular response could be elicited by smoking cubeb cigarettes. Wright and Moffat⁶ have made the same observation, using ashless filter paper cigarettes.

A third group of control experiments was conducted, in which the smoke was first passed through two water bottles or through a layer

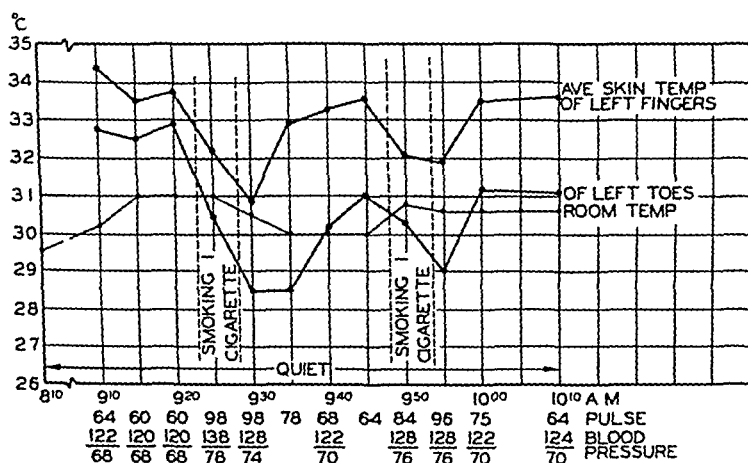


Chart 1—Effect of tobacco on the cutaneous temperature of a normal subject

of cotton impregnated with ferric chloride, both of which act as filters. The same cardiovascular changes occurred, but to a lesser degree.

Two cases of unquestionable thromboangitis obliterans were then investigated. In both there was marked reduction of the cutaneous temperature of the toes when a cigaret was smoked. In 1 case illustrated in chart 2, there was a marked difference in clinical signs of vascular deficiency between the two legs, the left having only feeble pedal and popliteal pulses and the right having a fair arterial thrust in the corresponding locations, nevertheless, there was a definite drop in the temperature of the foot with the far advanced arterial change. Lampson¹⁸ has verified these findings. A similar response to smoking has been described by Blotner¹⁸ in the case of a young man with

17 Mulinos, M. G., and Shulman, I. *Am J Physiol* **125** 310 1939

18 Blotner, H. *Ann Int Med* **9** 987 1936

diabetes and arteriosclerotic gangrene, the diagnosis being subsequently verified pathologically. One cannot assume, therefore, if clinically the great vessels are sclerotic, that the arterioles and capillaries are incapable of vasomotor changes, thus, as will be reiterated, tobacco is harmful to all persons with peripheral vascular deficiency without regard to age or to the status of the large vessels.

Fairly direct proof that nicotine absorbed in the act of smoking is the principle activating the vasospastic response was obtained by a fourth series of experiments, in which nicotine was administered intravenously. In a small group, nicotine hydrochloride given orally in doses of 1 mg in 30 cc of water, repeated every ten minutes for one hour, failed to produce any toxic effects. No cardiovascular response was noted. It was therefore deemed safe to administer intravenously 1 mg

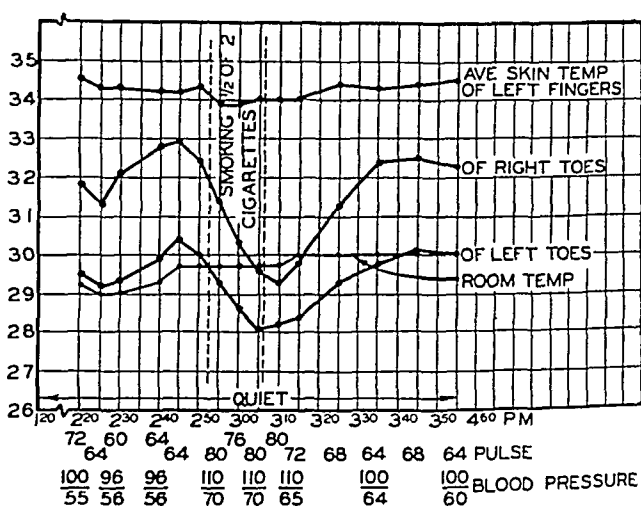


Chart 2—Effect of tobacco on the cutaneous temperature of a subject with thromboangitis obliterans

in the form of the tartiate or alkaloid. A solution was made up, 1 cc of saline solution containing 0.1 mg of the drug. The vasomotor reactions incident to pain and psychic stimulation associated with needling of the vein were obviated by adding a two way valve to the needle attachment of the buret. Ringer's solution was given slowly until a steady state had been reached, then 10 cc of saline solution was injected, without response, and was followed by Ringer's solution, which in turn was followed by the saline-nicotine solution. Ringer's solution was thereafter administered to the end of the observation period. Chart 3 fully illustrates the cardiovascular response obtained in this manner. There occurred, to a remarkably comparable degree, all the changes noted with the smoking of one cigaret.

The failure of large doses of nicotine administered by mouth to induce vascular responses can be explained only on the assumption

that in no given interval was there present in the general circulation an amount of alkaloid sufficient to constitute a threshold stimulus, and this may be either partly or largely due to relative slowness of absorption by the gastrointestinal tract

The question may well arise how an amount sufficient for a threshold stimulus can be absorbed by the mucous membranes of the mouth of a noninhaler, since the surface area and absorptive powers of the mucous membranes of the mouth are less than those of the gastrointestinal tract proper. The answer may be that the nicotine in smoke, being in a finely divided state, is far more easily assimilable than that in actual solution in water. An alternative explanation previously advanced,

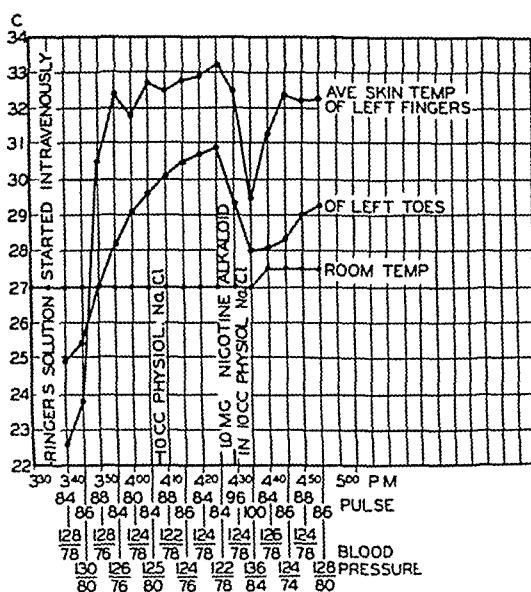


Chart 3—Effect of intravenously administered nicotine on the cutaneous temperature of a normal subject

based on the work of Biebl and his associates,¹⁹ is that when absorbed from the main gastrointestinal tract the substance is detoxified by the liver before it reaches the general circulation. However, recently Helmer and his associates²⁰ have succeeded in isolating nicotine from the urine of smokers in considerable amounts, the drug being present three to four days after the last smoke. Thus, not all the nicotine ingested could be so rapidly detoxified when given by mouth as to constitute the sole reason for the lack of response.

The fact that tobacco, by virtue of its nicotine content, produces peripheral vasospasm has thus been firmly established. This vasospasm

19 Biebl, M., Essex, H. E. and Mann, F. C. *Am J Physiol* **100** 167 1932

20 Helmer, O. M., Kohlstedt, K. G. and Page, I. H. *Am Heart J* **17** 15 1939

is associated with a decreased volume flow, as has been shown by the direct experiments of Lampson,¹⁶ Wright and Moffat⁶ and Euziere. The action in man is evidently mediated through the sympathetic nervous system, as has been shown by Maddock and his associates. Experiments conducted on a person on whom a cervicodorsal ramisection and ganglionectomy and a lumbar ganglionectomy for Raynaud's disease had been performed, abolishing the "sympathetic nervous control" to the extremities, showed the usual responses of the blood pressure and pulse to smoking, without any changes in cutaneous temperature of the extremities. Posterior tibial nerve block also prevented the vasospastic response in the temporarily enervated extremities of normal subjects, proving that the action is not peripheral. Whether or not the vasomotor center and the peripheral sympathetic ganglions are differentially stimulated in man has not been determined.

The role which the use of tobacco plays in the origin and clinical course of the peripheral vascular deficiencies may now be briefly considered. Tobacco has been indicted by many as the inciting cause of thromboangitis obliterans, without actual proof. Erb²¹ and later Silbert²³ maintained that it is responsible. Silbert stated that there had been, as far as he knew, no fully authenticated case of Buerger's disease in a nonsmoker. In over 1,000 cases which he observed there was not 1 patient who did not smoke. As to the effect of smoking on the course of the disease, it is general knowledge that continued smoking is associated with progressive circulatory deficiency in spite of the application of all known medical aids. Silbert stated that he had never seen a recurrence of the disease once it had been arrested by treatment unless the patient resumed smoking.

The manner in which tobacco is capable of inducing the pathologic process, if it actually is able to do so, is not known. Much work has been done on sensitization to tobacco in an attempt to solve the problem.

Harkavy and his associates²² and Sulzberger and Feit²³ have gone into the problem extensively. They concluded that a large percentage of persons suffering from Buerger's disease belong to the category of allergic persons and that the allergy is manifest to tobacco.²² Sulzberger and Feit²³ stated that thromboangitis obliterans must be classified as "a condition usually associated with a specific and marked hypersensitivity of the vascular apparatus of the skin to tobacco, but without any demonstrable connection with asthma." Nicotine-free extracts gave the reactions, whereas nicotine itself did not give a single unequivocal

21 Erb, W. *Munchen med Wchnschr* **51** 905, 1904

22 Harkavy, J., Hebal, S., and Silbert, S. *Proc Soc Exper Biol & Med* **30** 104, 1932

23 Sulzberger, M. B., and Feit, E. *J Immunol* **24** 425, 1933

reaction Maddock and his associates,²⁴ could not demonstrate any parallelism between the hypersensitiveness to tobacco extracts and the degree of vascular response to smoking. The question whether sensitization to tobacco is the prime factor in the causation of thromboangitis obliterans is still open.

The possibility that chronic vasospasm incident to the use of tobacco for long periods may in itself be highly important etiologically has likewise been neither proved nor disproved. It is known, however, that drugs unallied in structure to nicotine, namely, ergot²⁵ and posterior pituitary,²⁶ are capable of producing peripheral gangrene, thus it is conceivable that nicotine may occasionally do likewise. It is also possible that chronic vasospasm may simply be a strong contributing factor to the pathologic process which is maintained by some to be due to specific endarteritis. This may well represent the actual role of tobacco in the causation of thromboangitis obliterans.

Whether or not an actual causal relation between tobacco and thromboangitis obliterans can ever be established, it is an absolute necessity in the management of this disease to avoid the use of tobacco completely. The primary aim in the therapy of any acute peripheral vascular deficiency is to maintain a volume flow of blood sufficient to support metabolic processes in the diseased member until a collateral circulation can be sufficiently established to permit useful function. Obviously any drug as active as nicotine in producing a decreased blood flow in the extremities must be assiduously avoided, or treatment is useless. One might well say "Your legs or your cigarettes" and refuse to treat any patient with thromboangitis obliterans who continues to smoke. For the elderly person with arteriosclerotic peripheral vascular deficiency it is often difficult to stop smoking entirely, but it is desirable to reduce the use of tobacco as much as possible.

The use of patented filters and the so-called denicotinized cigarettes must likewise be prohibited, as there is at present voluminous proof that the filtering and denicotinizing processes are not adequate to prevent the vasospasm associated with smoking.²⁷

24 Maddock, W. G., Malcolm, R. L., and Collier, F. A. *Am. Heart J.* **12** 46, 1936.

25 Fabians, B. *Internat. Clin.* **3** 193, 1925.

26 Holsclaw, F. M., and Booth, J. A. *Arch. Pediat.* **42** 64, 1925.

27 Segal, H. L. *Am. J. M. Sc.* **196** 851, 1938. Wright and Moffat v. Maddock and Collier. *Lampson* 16.

SURGICAL INTERVENTION ON THE SYMPATHETIC NERVOUS SYSTEM FOR PERIPHERAL VASCULAR DISEASE

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Since the work of Royle and that of Hunter ¹ on the relation between the sympathetic nervous system and spastic paralysis, it has become obvious that a striking and persistent increase in blood flow follows interruption of sympathetic pathways to the extremities. Although previous attempts to increase peripheral blood flow by periarterial sympathectomy ² had been followed by transient improvement, lumbar sympathectomy as practiced by Royle ³ and by Hunter ¹ resulted in a more prolonged effect. This observation was the stimulus for extensive study of the relation between the sympathetic nervous system and the peripheral circulation. During the past fifteen years much has been learned about the anatomy and physiology of the sympathetic nervous system ⁴. Clinical application of this knowledge to the treatment of various peripheral vascular disorders now appears to be well established.

FUNDAMENTAL PRINCIPLES

Out of the tremendous amount of clinical and experimental evidence collected in the past decade has emerged the fact that certain fundamental principles must be observed in order to get the best clinical results. First, it seems clear that an operation to be successful must

From the Surgical Services and the Clinic for Peripheral Vascular Disease of the Massachusetts General Hospital

1 Hunter, J I. The Influence of the Sympathetic Nervous System in the Genesis of the Rigidity of Striated Muscle in Spastic Paralysis, *Surg, Gynec & Obst* **39** 721, 1924

2 Leriche, R. De l'elongation et de la section des nerfs perivasculaires dans certains syndromes douloureux d'origine arterielle et dans quelques troubles trophiques, *Lyon chir* **10** 378, 1913

3 Royle, N D. A New Operative Procedure in the Treatment of Spastic Paralysis and Its Experimental Basis, *M J Australia* **1** 77, 1924

4 White, J C. The Autonomic Nervous System, New York, The Macmillan Company, 1935. Gask, G E, and Ross, J P. The Surgery of the Sympathetic Nervous System, Baltimore, William Wood & Company, 1934. Livingston, W K. The Clinical Aspects of Visceral Neurology, Springfield, Ill, Charles C Thomas, Publisher, 1935

be thorough in its interruption of sympathetic motor fibers to the part in question. Second, an operation on the sympathetic nervous system must interrupt either preganglionic or postganglionic pathways or a combination of the two. The best results have been obtained by interruption, as far as possible, of preganglionic fibers only. In the third place, time has demonstrated conclusively the tremendous regenerative power of interrupted sympathetic nerves. In order to give satisfactory late results, an operation must be done in such a way as to eliminate or minimize the possibility of regeneration. Space does not permit a summary of the evidence at hand, but adequate reference is made to articles dealing with these matters.⁵

CASES IN WHICH SYMPATHECTOMY IS INDICATED

If in a given case impaired blood flow to the extremity is entirely a question of vascular spasm, as in the early stages of Raynaud's disease, sympathectomy will yield its most brilliant result. By contrast, if the vascular insufficiency is the result of chronic obliterative vascular disease, as in advanced arteriosclerosis with associated diabetes, sympathectomy will not be helpful. Many patients, however, suffer from a lesion which is both obliterative and vasospastic, in which case sympathectomy may be helpful. Thromboangitis obliterans is representative of such a lesion.

Although the primary effect of sympathectomy is probably largely the result of vasomotor paralysis, another factor must be considered. Sympathectomy results in sudomotor paralysis in addition to vasomotor paralysis. A portion of the effect on the periphery is therefore due to inactivation of the sweat glands.

It becomes clear, then, that studies which enable one to evaluate the vasomotor and sudomotor components in a given case are of primary importance. By their use one can best predict the effect of operation.

5 (a) Elliott, T. R. The Action of Adrenaline, *J. Physiol.* **32** 401, 1905. (b) Cannon, W. B., and Uridil, J. E. Studies on the Conditions of Activity in Endocrine Glands. VIII. Some Effects on the Denervated Heart of Stimulating the Nerves of the Liver, *Am. J. Physiol.* **58** 353, 1921. (c) Cannon, W. B., and Rosenbluth, A. Studies on Conditions of Activity in Endocrine Organs. XXIX. Sympathum E and Sympathum I. *ibid.* **104** 557, 1933. (d) Freeman, N. E., Smithwick, R. H., and White, J. C. Adrenal Secretion in Man. The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy to Adrenalin and to Adrenal Secretion Resulting from Insulin Hypoglycemia. *ibid.* **107** 529, 1934. (e) Smithwick, R. H., Freeman, N. E., and White, J. C. Effect of Epinephrine on the Sympathectomized Human Extremity. An Additional Cause of Failure of Operations for Raynaud's Disease, *Arch. Surg.* **29** 759 (Nov.) 1934. (f) Ascroft, P. B. The Basis of Treatment of Vasospastic States of the Extremities. An Experimental Analysis in Monkeys. *Brit. J. Surg.* **24** 787, 1937.

Such tests are also important in evaluating the result of operation as regard to both completeness and permanence. Those more useful and most commonly employed will be considered.

CONDITIONS FOR STUDY

The relation between the surface temperature of an extremity and the room temperature is important. Cold is a great stimulus to peripheral vasoconstriction. Pain and emotion may also be utilized, but changes in temperature are better controlled. The optimum room temperature for use in clinical studies is approximately 68 F. This should be relatively constant during the period of observation and for this reason a constant temperature room with controlled humidity is desirable. It is not however absolutely essential. Much of clinical value can be learned without it.

It is characteristic of a vasospastic disorder that the surface temperature of a finger tip or a toe tip will be slightly lower than the room temperature if sufficient time is allowed for adjustment to take place. When obliterative vascular disease predominates the extremity does not, as a rule, cool quite to room temperature and rarely falls below it.

When the surface temperature has become stabilized in relation to the room temperature one can utilize a number of indirect methods of estimating the increase in blood flow. After inhibition of vasoconstriction the resulting increase of surface temperature under condition of constant room temperature can be measured with a thermocouple or better by a potentiometer indicator.

METHODS OF STUDYING VASOMOTOR ACTIVITY

Vasoconstriction can be reflexly inhibited by warming the trunk or by immersion of the opposite extremities in warm water. Vasoconstriction can also be inhibited by induction of fever by intravenous injection of foreign protein (typhoid vaccine). The resulting rise in

6 Lewis T. and Pickering G. W. Vasodilatation in the Limbs in Response to Warming the Body with Evidence for Sympathetic Vasomotor Nerves in Man. *Heart* 16:33 1931.

7 Gibson J. H. Jr. and Lannis E. M. Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water. *J. Clin. Investigation* 11:1019 1932.

8 Brown G. E. The Treatment of Peripheral Vascular Disorders of the Extremities. *J. A. M. A.* 87:379 (Aug. 7) 1926. Allen A. W. and Smith R. H. Use of Foreign Protein in the Treatment of Peripheral Vascular Diseases. Results of Intravenous Injections of Typhoid Vaccine. *Ibid.* 91 (Oct. 20) 1928.

surface temperature of the extremity makes it possible to estimate the vasomotor index. All three of these methods have been used extensively.

Vasoconstriction can be eliminated also by blocking the efferent vasomotor pathway with procaine hydrochloride. This test perhaps provides a better index of the result to be expected from sympathectomy, because the sudomotor pathway is also temporarily interrupted. Although paravertebral block of the sympathetic supply to the arm and leg with procaine hydrochloride is an excellent method, peripheral nerve block is more practical, almost as accurate and far easier for the average person to perform.⁹

Thus, for the hand the ulnar nerve is most frequently blocked at the elbow. This results in almost maximal vasodilation in the anesthetic area. Injection of the anesthetic into the median and radial nerves as well may result in a slight further increase in surface temperature, but not enough to make the procedure necessary in a routine test.

The foot may be temporarily denervated by block of the posterior tibial nerve at the ankle and the common peroneal nerve just below the head of the fibula with procaine hydrochloride. Injection of the anesthetic into the sciatic nerve in the gluteal region may be utilized as an alternative method. Spinal anesthesia is a satisfactory but slightly more dangerous method of causing temporary inhibition of vasoconstriction in the lower extremity.

In all of the tests mentioned so far, the increase in blood flow is indirectly measured by the rise in surface temperature of the tip of a finger or of a toe. In the presence of purely vasospastic disorders this increase will amount to as much as 25 degrees (F). If obliterative vascular disease is the predominating factor, there may be little or no rise in surface temperature. If a combination of spasm and obliteration exists, changes in temperature of from 5 to 15 degrees (F) are commonly seen.

Other indirect methods of estimating increased blood flow after inhibition of sympathetic influence are utilized. The finger or toe plethysmograph is a satisfactory and sensitive apparatus.¹⁰ Hand and

⁹ White, I. C. Diagnostic Blocking of Sympathetic Nerves to Extremities with Procaine, *J. A. M. A.* **94** 1382 (May 3) 1930, Diagnostic Novocaine Block of the Sensory and Sympathetic Nerves. A Method of Estimating the Results Which Can Be Obtained by Their Permanent Interruption, *Am. J. Surg.* **9** 264, 1930. Morton, I. J., and Scott, W. J. M. Methods for Estimating the Degree of Sympathetic Vasoconstriction in Peripheral Vascular Disease. *New England J. Med.* **204** 955, 1931.

¹⁰ Bolton B., Carmichael F. A., and Sturup G. Vasoconstriction Following Deep Inspiration. *J. Physiol.* **86** 83, 1930.

foot calorimeters may be used¹¹ Their use is too complicated, however, for the average clinician

Changes in blood flow may also be quantitated by the hand plethysmograph By this instrument the volume of blood flow per minute per unit of tissue volume may be measured fairly accurately under varying conditions The method has been described by Freeman,¹² who has used it effectively Much experience is required to use and interpret the results of this test correctly

The photoelectric cell offers a sensitive method¹³ of studying the effect of vasoconstriction Instead of cooling the extremity, one places the patient in a warm atmosphere, which is conducive to vasodilation The level of blood flow through a translucent portion of the finger tip is recorded photographically, and the reflex vasoconstrictor response is then determined Various stimuli may be used, such as a deep breath, immersion of the opposite hand in ice water, sudden noise or an unpleasant suggestion Many extremities have been tested for me by Finesinger¹⁴ both before and after various operative procedures (fig 1) The test has proved invaluable not only in estimating the effect of the intact sympathetic system on peripheral blood flow but in testing the completeness of interruption of the sympathetic nerve supply by various operations

A study of cutaneous resistance¹⁵ as an index of sweat gland activity is helpful in estimating activity of the sympathetic nervous system before and after operation (fig 2) The level in ohms is important, but the reflex response to a stimulus, such as a sudden noise, is even more illuminating I have found this test to be one of the most delicate and useful of all It is helpful in studying the completeness of sympathectomy and the state of "relapse" Many records of its use have been made for me by Finesinger,¹⁶ who has also made observations by these

11 Kegerreis, R Calometric Studies of the Extremities II Experimental Apparatus and Procedures, *J Clin Investigation* **3** 357, 1927

12 Freeman, N E The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am J Physiol* **113** 384, 1935

13 Hertzman, A B Photoelectric Plethysmography of Fingers and Toe in Man, *Proc Soc Exper Biol & Med* **37** 529-534, 1937, Comparative Estimation of Blood Supply of Skin Areas from Photoelectrically Recorded Volume Pulse, *ibid* **38** 562-564, 1938

14 Finesinger, J E, Hensner, A P, and Smithwick, R H Vasomotor Studies in Raynaud's Disease Before and After Sympathectomy, *Tr Am Neurol A* **65** 193, 1939

15 Landis, C Electrical Phenomena of the Skin (Galvanic Skin Response), *Psychol Bull* **29** 693, 1932

16 Finesinger, J E Unpublished data

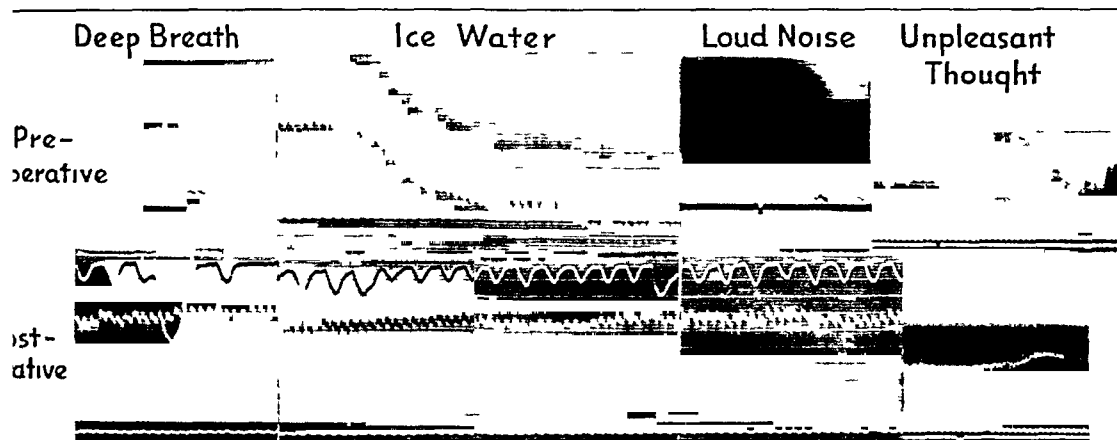


Fig 1—Blood flow through a translucent portion of the finger tip. Variations in blood flow are detected by the photoelectric cell, which lies beneath the finger tip, through which a beam of light passes. A fall in the blood flow level on the photograph denotes vasoconstriction, a rise, vasodilatation. The individual pulse oscillation can be seen on the records, more clearly after sympathectomy. The characteristic responses to various stimuli are shown. After a complete sympathectomy, these are abolished. Stimuli were a deep breath, a loud noise, immersion of the opposite hand in ice water and an unpleasant suggestion.

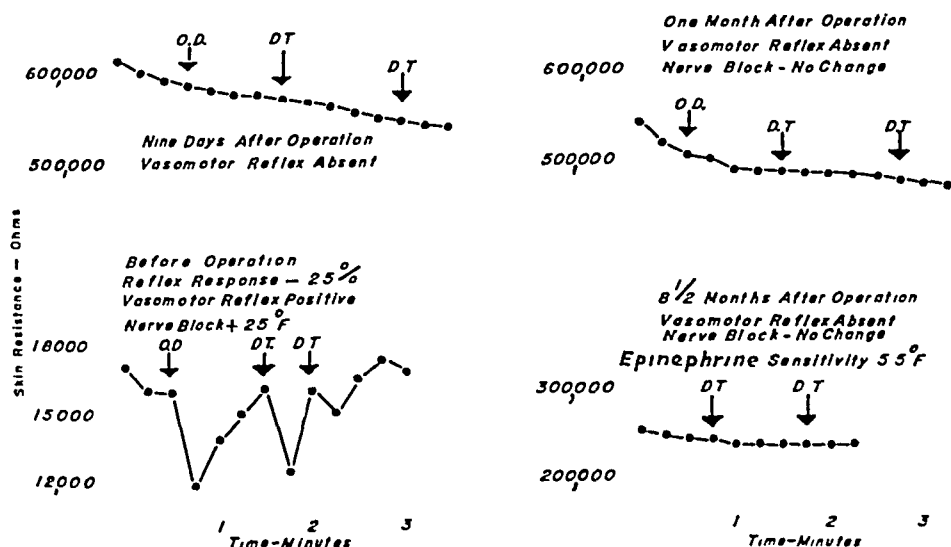


Fig 2—Typical record of cutaneous resistance. Before operation the level is low and variable and a sharp fall in response to a sudden stimulus is noted. Opening the door of the room in which the patient lay or dropping a tin on the floor was the stimulus used. After a complete sympathectomy the level of cutaneous resistance is high and constant and reflex response is abolished. It should be noted, however, that as time goes on there is a slow fall in the level of cutaneous resistance. Because the level is not variable and reflex response is abolished, it seems most likely that this fall is due to a peripheral mechanism and is not of central origin.

methods of both vasomotor and sudomotor reflex responses in a study of normal and of psychotic persons

All of the forms of study which have been mentioned have been utilized in this clinic. The simplest and most practical of all is peripheral nerve block, my associates and I use this routinely. Of the other tests, the study of reflex vascular response by the photoelectric cell method and the study of changes in cutaneous resistance by the Wheatstone bridge and the psychogalvanic reflex have proved most valuable. These two studies have enabled us to separate activity of the sympathetic nervous system into its vasomotor and its sudomotor components¹.

It must be stated, however, that clinical observation and judgment must be combined with the results of the various tests in making a final decision as to the indications for sympathectomy in a given case. This applies particularly to cases in which both obliterative and vasospastic elements are present. Not uncommonly, under these circumstances, one cannot demonstrate any improvement in blood flow after interruption of sympathetic outflow by block with procaine hydrochloride. Yet one may suspect from clinical observation that a definite element of vascular spasm is present, as judged by cold, moist extremities with "multiple phase color changes." Frequently sympathectomy has resulted in a marked rise in surface temperature under these circumstances. Study of reflex vasomotor and sudomotor activity before operation will often demonstrate a marked response when there is none to peripheral nerve block. This is probably due to the fact that the latter test is carried out under conditions promoting vasoconstriction. Thus, it seems probable that a constricted arteriole with some organic change will not necessarily relax, when vasoconstriction is inhibited by procaine hydrochloride, as long as it is in a cool environment. Vasoconstriction may persist as a purely local response to cold. When, however, the same extremity is studied in a warm room, the ability of the vessels to constrict in a surprising fashion can often be demonstrated by the reflex vasomotor responses.

For this reason my associates and I routinely use both peripheral nerve block and studies of reflex vascular and sweat gland activity. As has been stated, however, the final decision for or against sympathectomy must be based on clinical judgment and experience as well as on objective tests.

CHANGES AFTER SYMPATHECTOMY

1 *When Operation is Complete*—Interesting and characteristic changes take place after preganglionic sympathectomy. The findings vary with the time which has elapsed since operation. There seem to be

17 Darrow, C. W. The Galvanic Skin Reflex, not a Vasoconstrictor Phenomenon, *Psychol. Bull.* 26 155, 1929

certain phases through which the extremity passes. It is therefore best to divide the discussion into three parts, namely, changes observed during the first week, changes observed during the second and third weeks, and late changes (observed months or years after operation)

(a) Changes During the First Week. On the day after sympathectomy, the extremity appears to be dry, warm and of excellent color. The level of surface temperature is high and would presumably not rise further on block with procaine hydrochloride. The level of cutaneous resistance is high, and reflex sweat gland activity as well as vasomotor activity is thought to be abolished. Between the third and the fifth day a curious clinical phenomenon takes place. The extremity suddenly begins to perspire, becomes cooler and often is discolored. These changes may be obvious or may be detected only by careful testing. The sudden burst of sympathetic nervous activity gradually disappears, so that by the end of a week it has vanished. During this phase there is a fall in surface temperature and in the level of cutaneous resistance. If the peripheral nerves are blocked with procaine hydrochloride during the height of the reaction, a rise in cutaneous temperature will follow. As reflex vasomotor and sudomotor activity are known to be absent during this period, it would seem that there is an actual spontaneous outflow of sympathetic impulses from the decentralized sympathetic ganglions.¹⁸ These changes are shown in figures 3, 4 and 5.

(b) Changes During the Second and Third Weeks. Between the first and the second week after operation the level of cutaneous resistance reaches its high point. The surface temperature falls slowly for two or three weeks after operation, then it strikes a level.¹⁹ The highest readings are usually obtained the first day after operation. During the second week, the phenomenon of sensitivity to epinephrine and similar substances appears. This is complete between two and three weeks after operation and is probably largely responsible for the fall in surface temperature. This matter has previously been discussed in detail.²⁰ Thus, by the end of three weeks the extremity may be said to have become stabilized (figs. 3, 4 and 5).

18 GÖRERTS, I. Contribution à l'étude de l'innervation sympathique du cœur, *Arch. internat. de med. exper.* **11** 629, 1936. Tower, S. S. and Richter, C. P. Injury and Repair Within the Sympathetic Nervous System. III. Evidence of Activity of Postganglionic Sympathetic Neurons Independent of the Central Nervous System, *Arch. Neurol. & Psychiat.* **28** 1149 (Nov.) 1932. Simone, F. A. The Effect of Regeneration of the Nerve Supply on the Sensitivity of the Denervated Nictitating Membrane to Adrenaline. *Am. J. Physiol.* **120** 466, 1937.

19 Richter, C. P. The Nervous Control of the Electrical Resistance of the Skin. *Bull. Johns Hopkins Hosp.* **45** 56, 1929.

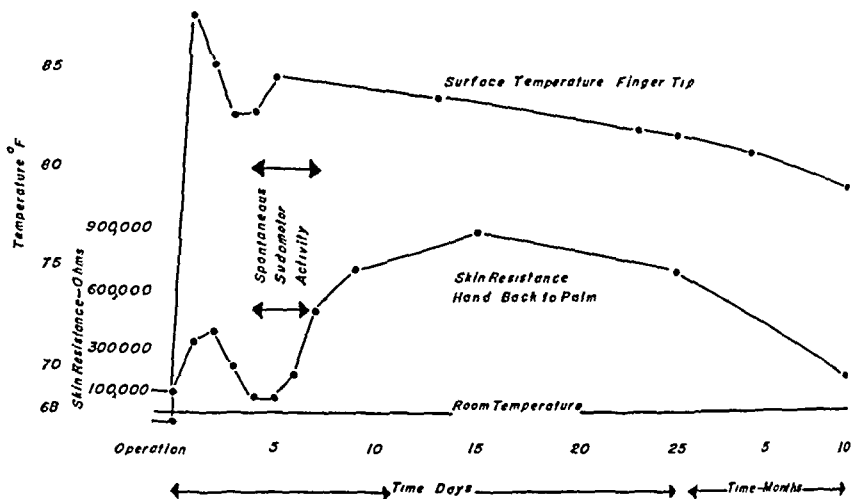


Fig 3—Diagrammatic representation of the changes noted in the surface temperature level of the finger tip and in the cutaneous resistance level of the hand. It is a composite chart of the average findings in a group of denervated upper extremities as days, weeks and months passed after operation. It is presented to bring out the nature of the curve rather than the actual levels. The period of "spontaneous sympathetic activity" is shown, together with the fall in surface temperature and cutaneous resistance levels at this time. Both reflex vasomotor and sudomotor activity are abolished during this period, as after it and presumably before it.

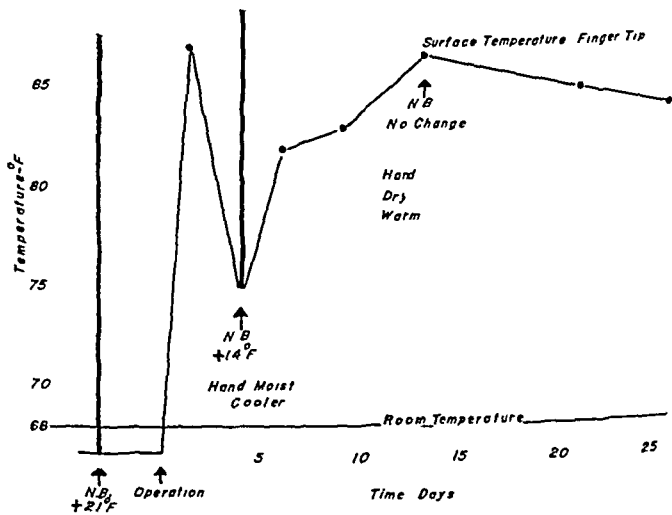


Fig 4—Level of surface temperature after operation on an upper extremity. It was obtained by plotting daily readings against time and room temperature. The characteristic fall in surface temperature between the third and the sixth day is shown. Block of the ulnar nerve at the low point by injection of procaine hydrochloride was followed by a sharp rise in surface temperature. This suggests that sympathetic motor impulses were passing peripherally from the decentral ganglions, because reflex vasomotor and sudomotor responses were absent. During this phase, the hand was cool, moist and often discolored. The phenomenon disappeared, clinically at least, by the end of the first week. There was no rise in surface temperature of the finger tip when the ulnar block was repeated on the thirteenth postoperative day.

(c) *Changes Months or Years After Operation* As the extremity is observed during the following months or years, little significant change takes place. There seems to be a slight fall in the level of surface temperature as time goes on. There is a more definite fall in that of cutaneous resistance, in spite of the fact that reflex sweat gland activity is abolished.²⁰ This may be due to independent activity of the sweat glands or may be a humoral response. Thus, a well sympathectomized extremity months or years after the operation should have a high surface temperature with little or no rise on block with procaine hydrochloride, a much higher level of cutaneous resistance than before operation, without evidence of reflex response, and complete abolition of reflex vasomotor activity, as evidenced by photoelectric cell studies (fig 2)

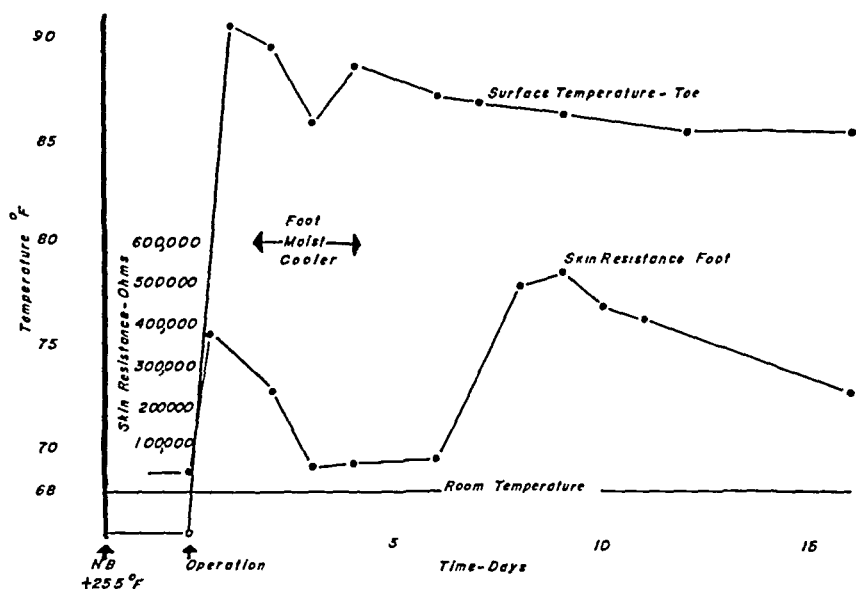


Fig 5—Daily surface temperature and cutaneous resistance readings, plotted for two weeks after complete denervation of the lower extremity. The curves are similar to those noted for the upper extremity. The same phase of lowered temperature and cutaneous resistance levels accompanied by clinical evidence of moisture and coolness is brought out. Note the sharp fall in cutaneous resistance during the second week. As reflex sudomotor activity is abolished completely, this cannot be utilized as evidence of either incomplete sympathectomy or regeneration. It may be some peripheral mechanism (perhaps humoral) affecting the sweat glands directly.

20 Richter, C. P. A Study of the Electrical Skin Resistance and the Psychogalvanic Reflex in a Case of Uni-Lateral Sweating, *Brain* 50:216, 1927. Solomon, P. The Psychogalvanic Reflex. Applications to Neurology and Psychiatry. *Arch Neurol & Psychiat* 34:818 (Oct) 1935.

There should be a slight drop, of about 5 degrees (F), in surface temperature in response to epinephrine

Occasionally a rise of 1 to 3 degrees (F) in surface temperature is noted on peripheral nerve block in the absence of evidence of reflex sudomotor or vasomotor activity. This may be the result of a continued slight discharge of impulses from the decentralized ganglions (fig 6)

2 *When Operation Is Incomplete*—There is a marked difference between the results of complete and those of incomplete interruption of sympathetic impulses to an extremity. If the operation is only partially effective, the level of surface temperature may be changed little if any. Hence, peripheral nerve block will result in a marked rise in

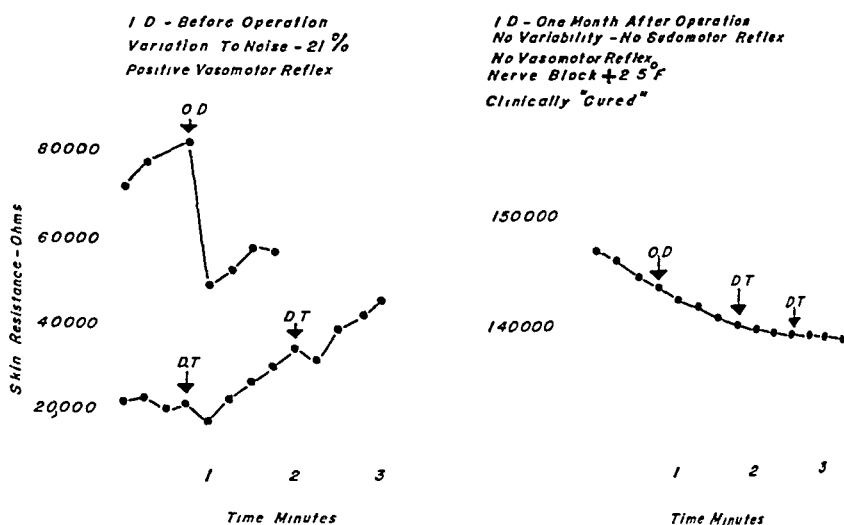


Fig 6—Chart demonstrating how occasionally one notes a slight rise in surface temperature of a finger tip following peripheral nerve block after an apparently complete sympathectomy, as evidenced by abolition of vasomotor and sudomotor reflexes. This chart should be compared with figure 2, which shows the usual result. This slight rise in surface temperature following peripheral nerve block is perhaps best explained by assuming persistence of some efferent sympathetic motor activity arising in the decentralized ganglions. It does not appear to be of any clinical significance.

cutaneous temperature. The level of cutaneous resistance will be low, and reflex sweat gland activity will be present. Reflex vasomotor responses will persist. Sensitivity to epinephrine will not appear. The effect of incomplete sympathectomy in terms of surface temperature is shown in figure 7. The case illustrated was very helpful to me in my early attempts to find an adequate preganglionic type of operation for the upper extremity.

3 *When "Relapse" Takes Place*—This subject has been well discussed by Simmons and Sheehan²¹ The term as they used it is descriptive It implies a state of affairs which occurs six months to a year and a half after what was thought to be a complete operation It implies also that the symptoms are not quite the same as before operation The condition occurs after both preganglionic and postganglionic types of sympathectomy The explanation has not been wholly clear

The patient notices that after a period of relief or improvement the extremity begins to be cooler and also to perspire Slight changes in color may occur, but the symptom complex does not seem to be as severe as before operation This situation is undoubtedly due to partial regen-

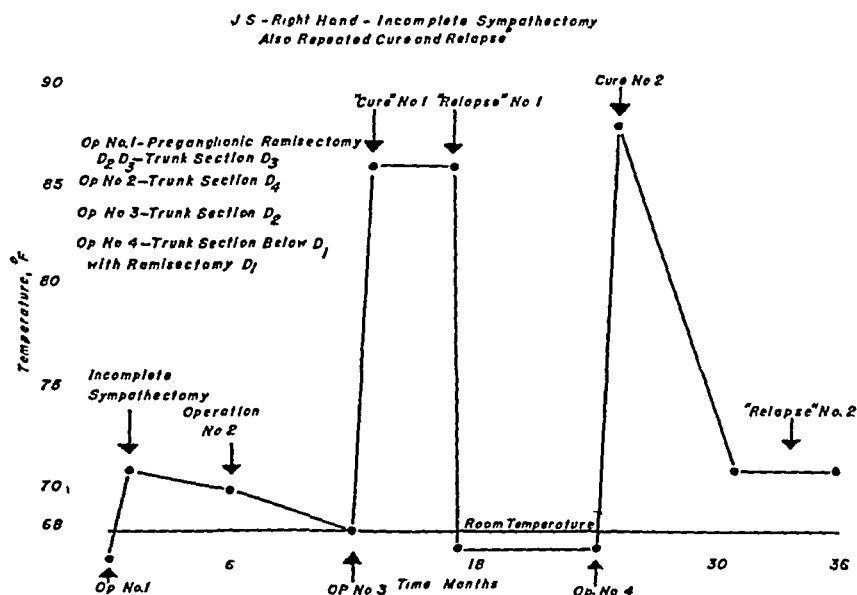


Fig 7—Case of J S The ability of a finger tip to maintain a high surface temperature level in a cool environment may be utilized in judging the completeness of sympathectomy The first two operations failed to denervate the hand because the white rami from the second and third dorsal segments were not actually divided This was temporarily corrected by operations 3 and 4 "Relapse" due to regeneration occurred, however, after both of these procedures

eration of sympathetic fibers The effect of repeated "relapse" in terms of surface temperature is shown in figure 8 The case illustrated was also extremely helpful to me in working out an operation for the upper

21 Simmons, H T, and Sheehan, D An Inquiry into "Relapse" Following Sympathectomy, *Lancet* 2 788, 1937

extremity which would be adequately complete, preganglionic and not followed by regeneration or "relapse"

In most studies of the state of "relapse," reflex sweating has been used as evidence of regeneration of vasomotor fibers. I have had occasion to observe a number of extremities in which there has been a "relapse" and to study reflex sweat gland activity and reflex vascular response separately. This has been done by utilizing cutaneous resistance readings and the psychogalvanic reflex in the former and reflex photoelectric cell responses in the latter instance.

It was found (table 1) that the vasomotor reflex was absent in all of 8 "relapsed extremities" after either preganglionic or postganglionic operations.

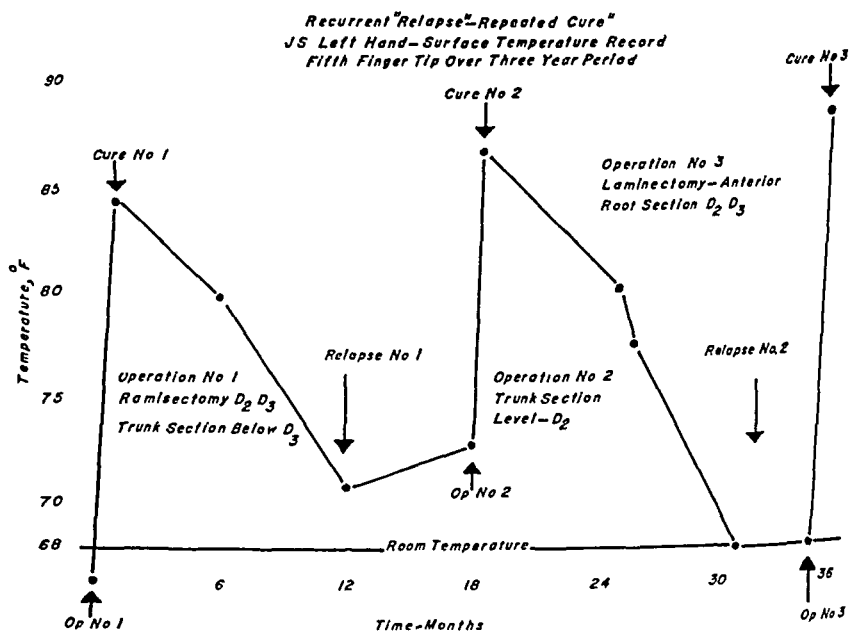


Fig 8—Chart indicating that section of the rami and division and displacement of the nerve trunk are not adequate assurance against regeneration in the case of the upper extremity. This upper extremity was well denervated twice, but regeneration occurred and "relapse" resulted. Several similar experiences convinced me that the anterior roots of the second and third dorsal nerves must be divided to prevent this occurrence. (See figure 11)

In table 2, data on reflex sweat gland activity in 5 of these cases are presented. A fall in the level of cutaneous resistance in response to an adequate stimulus was present in each instance in a degree comparable to that seen in the average untreated extremity. This was true regardless of the type of operation which had been performed (fig 9). This reflex was abolished after further surgical intervention had been undertaken to interrupt regenerated pathways (fig 10). In table 3, other changes in the state of "relapse" are contrasted with the findings in the

TABLE 1—*I somotor Activity in Eight Cases of Relapse (Upper Extremity)* *

Patient	Hand	Degree of Relapse	Operation	Time Since Operation Mo	Vasomotor Reflex
J S	Right	Mild	Ramsectomy	30	Absent
D McG	Left	Mild	Ramsectomy	27	Absent
J S	Left	Moderate to marked	Ramsectomy	30	Absent
Alves	Right	Moderate to marked	Ramsectomy	10	Absent
Alves	Left	Moderate to marked	Ramsectomy	10	Absent
A McJ	Left	Moderate to marked	Ramsectomy	24	Absent
A McG	Right	Moderate to marked	Ganglionectomy (C ₂ , D ₁ , D ₂)	65	Absent
P B	Left	Moderate to marked	Ganglionectomy (D ₁ , D ₂)	97	Absent

* No reflex response was demonstrated in any instance by the photoelectric cell method regardless of the type of operation. All the operations were believed to have been originally complete.

TABLE 2—*Reflex Sweat Gland Activity in Five Cases of "Relapse" (Upper Extremity)* *

Patient	Hand	Degree of Relapse	Operation	Time Since Operation, Mo	Cutaneous Resistance Ohms	Reflex Response	Vasomotor Reflex
J S	Right	Mild	Ramsectomy	30	125 000	8%	Absent
D McG	Left	Mild	Ramsectomy	27	74 000	15%	Absent
J S	Left	Moderate to marked	Ramsectomy	30	100 000	13%	Absent
A McG	Left	Mild	Ramsectomy	24	30 000	22%	Absent
A McG	Right	Mild	Cervicodorsal ganglionectomy	65	35 000	10%	Absent
After Secondary Operation							
J S	Left	"Cured"	Laminectomy anterior root section (D ₁ , D ₂)	1	190,000	Absent	Absent

* No reflex vasomotor activity could be detected by the photoelectric cell method. The reflex sweat gland activity was abolished in 1 of these extremities after further operation had interrupted regenerated nerve pathways.

TABLE 3—*Comparison of Data on a "Relapsed" and Data on a "Cured" Upper Extremity* * After Interruption of Regenerated Sympathetic Pathways

	Symptoms	Rise in Temperature with Ulnar Block	Fall in Temperature on Intravenous Administration of Epinephrine	Vasomotor Reflex	Cutaneous Resistance Level	Variability	Reflex
Relapsed	Marked	13 degrees F	2 degrees F	Absent	100,000	Marked	Positive 13%
"Cured" 1 mo after operation	None	18 degrees F	8.5 degrees F	Absent	190 000	None	Absent

* Left hand of patient J S

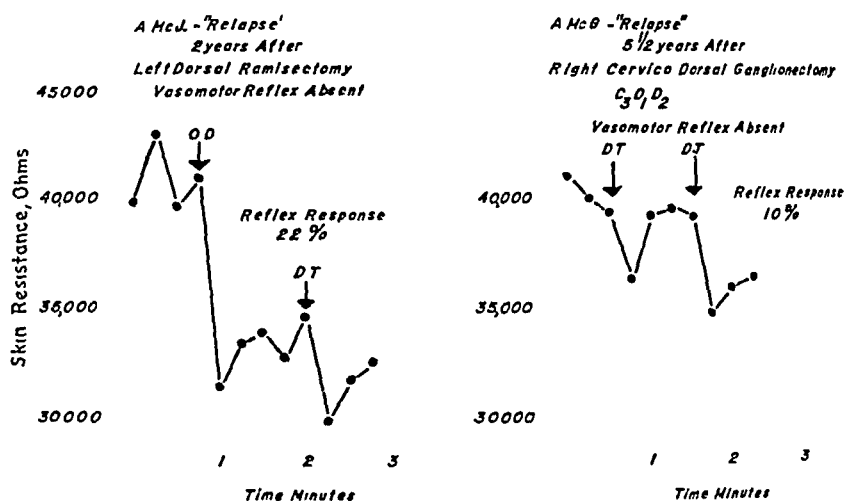


Fig 9—Low, variable levels of cutaneous resistance with positive reflex response years after what was believed to have been a complete denervation. In one case a preganglionic ramisectomy had been performed, in the other, a ganglionectomy. The picture represented by this chart is comparable to that seen before operations as far as changes in cutaneous resistance are concerned. Note, however, that no reflex vasomotor response was demonstrated by the photoelectric cell in either instance.

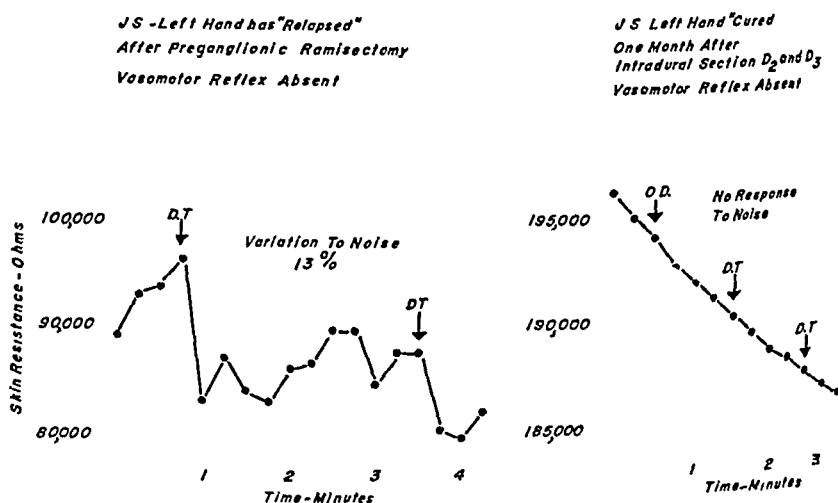


Fig 10—Chart showing that further operation after "relapse" results in a higher, constant level of cutaneous resistance without reflex response. The vasomotor reflex as judged by the photoelectric cell method was absent both in the "relapsed" and in the "cured" state.

same extremity after the symptoms had been completely relieved by further surgical procedures

These observations indicate that in the state of "relapse," reflex activity of the sweat glands is present in a degree comparable to that seen when operation has not been performed. The vascular reflex, however, could not be demonstrated by the same technic (photoelectric cell) which always produced a response in the normally innervated extremity. Further study will be necessary to determine the accuracy and significance of these findings.

OPERATIVE TECHNIC

The foregoing summary of changes noticed after various operations on the sympathetic nervous system is given primarily to show why I use the type of operation to be described. The difficulties encountered apply

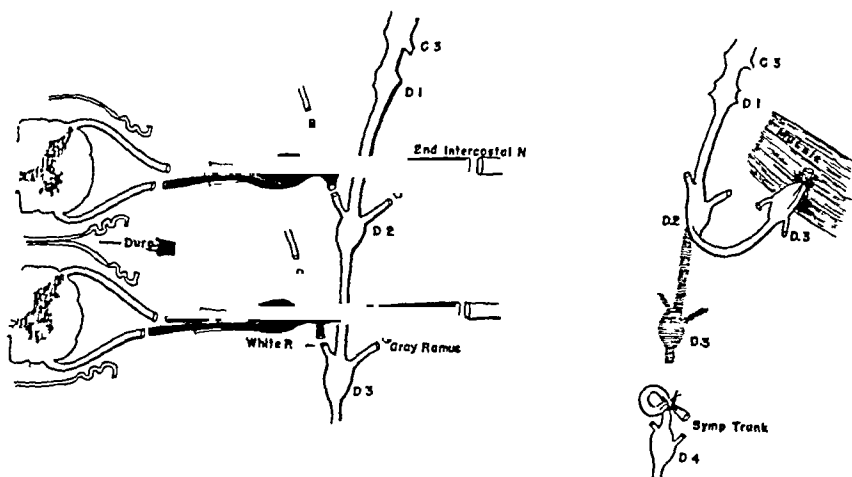


Fig 11—Diagrammatic representation of what is done to interrupt the sympathetic outflow from the second and third dorsal segments in order to prevent regeneration. The impulses from the lower dorsal levels are interrupted by dividing the trunk below the third dorsal ganglion and ligating the distal divided end. The proximal divided end is brought out of the thorax and sutured into the wound to prevent regeneration from this source. The outflow from the first dorsal segment is not interrupted because it is insignificant in amount and cannot be permanently abolished without sacrificing the first dorsal motor root. This would result in motor weakness in the extremity. Exposure is obtained by resecting the inner portion of the third rib and the tip of the transverse process through a small vertical paravertebral incision. The pleura is separated from the thoracic cage over an appropriate distance. See other references for more detailed description of the operation. An operation, similar in principle, utilizing an anterior approach, has been described (Telford, E. D. *The Technique of Sympathectomy*, Brit J Surg **23** 448, 1935).

almost wholly to the upper extremity. It never has been a problem to produce an adequate, lasting and preganglionic type of operation for the lower extremity.

These operations have been described in great detail elsewhere. The operation for the arm (fig 11) and that for the leg (fig 12) are described briefly.

CLINICAL RESULTS

Table 4 is a summary of clinical results following sympathetic denervation of the upper extremity by the method described (root section). Also included are earlier cases in which operation (ramisection) was performed. The results in these cases were not as good, and this led to the development of the present technic, which appears

TABLE 4—*Clinical Results for Upper Extremity**

	No of Extrem- ities	Excellent Clinical Result	Improved	Unimproved
Group I				
All operations	33	28 (84%)	3 (10%)	2 (6%)
Ramisection	6	1 (17%)	3 (50%)	2 (33%)
Root section	27	27 (100%)		
		Very Good Clinical Result	Improved	Unimproved
Group II				
All operations	34	25 (73.5%)	8 (23.5%)	1 (3%)
Ramisection	10	5 (50%)	4 (40%)	1 (10%)
Root section	24	20 (83.3%)	4 (16.7%)	
		Good Clinical Result	Improved	Unimproved
Group III				
All operations	26	12 (46%)	12 (46%)	2 (8%)
Ramisection	9	2 (22.5%)	5 (55%)	2 (22.5%)
Root section	17	10 (58.8%)	7 (41.2%)	

* The results of various types of preganglionic operations are given in this table. The best results were those following root section as illustrated in figure 11. All cases in this table are examples of primary vascular spasm. They are grouped according to the degree of local fault present before operation (see text).

satisfactory. The cases are arranged in three groups, according to the degree of local fault already present. There was no obvious local fault in the cases in group I. There were definite cutaneous changes in the extremities in group II (scleroderma), but no roentgen change. Group III contained cases of advanced scleroderma and definite roentgen changes, such as calcification of soft tissues or destruction of bone.

22 Smithwick, R. H. Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity. Preliminary Report, *Ann Surg* **104** 339, 1936, The Value of Sympathectomy in the Treatment of Vascular Disease, *New England J Med* **216** 141, 1937, The Sympathetic Nervous System and Vascular Disease, in Blumer, G. The Practitioner's Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1938, vol. 13. The Rationale and Technique of Sympathectomy for the Relief of Vascular Spasm of the Extremities, *New England J Med*, to be published.

of the terminal phalanges. The untoward effect on the end result of the degree of local fault already present is clearly shown.

Table 5 includes data on a group of cases in which the vascular spasm of the upper extremity was secondary to some underlying disease. The results in this group are comparable to those obtained in group III, table 1.

Table 6 represents a consecutive series of denervated lower extremities. The extraperitoneal approach was utilized in every instance. The cases are divided into two groups, depending on whether the vasospasm was primary or secondary.

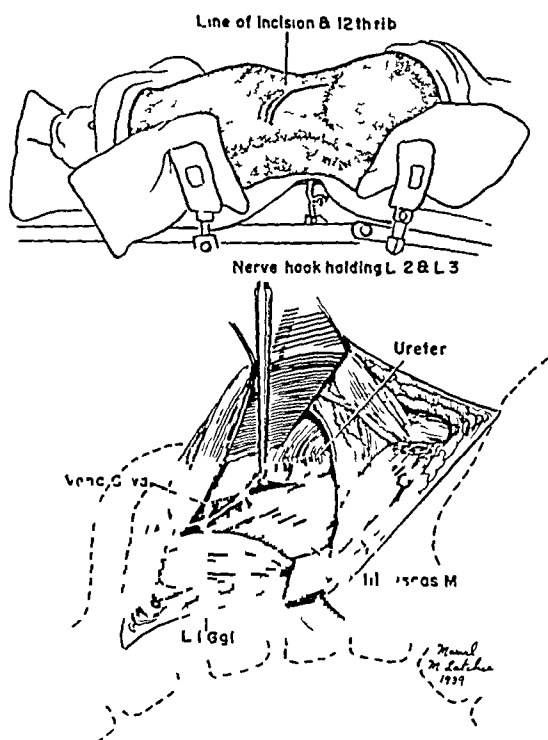


TABLE 5—*Clinical Results for Upper Extremity (Group 4*)*

Diagnosis and Treatment	No of Cases	No of Extremities	Excellent Result	Improved	Unimproved
Rheumatoid arthritis with vascular spasm	5	7	3	2	2
Ramisection		4		2	2
Anterior root section		3	3		
Causalgia with vascular spasm anterior root section	2	2	2		
Hypertension, marked vascular spasm after splanchnic resection, anterior root section	1	2	2		
Thrombosis of brachial artery with scalenus syndrome	2	3	3		
Ramisection		2	2		
Anterior root section		1	1		
Arteriosclerosis with gangrene and ulceration	6	10	4	5	1
Ramisection		6	2	4	
Anterior root section		4	2	1	1
Thromboangitis obliterans with ulceration and gangrene	4	4		4	
Ramisection		3		3	
Anterior root section		1		1	
Totals	20	28	12 (42.9%)	13 (46.4%)	3 (10.7%)

* A miscellaneous group in which some obliterative vascular disease was present in many instances or in which the vascular spasm was secondary to some underlying condition

TABLE 6—*Clinical Results for Lower Extremity**
(May 26, 1936 to March 22, 1939)

Diagnosis	No of Cases	No of Extremities	Excellent Result	Improved	Unimproved
A Vasospastic Disorders					
Raynaud's disease	9	18	18		
Vascular spasm and old poliomyelitis	2	3	3		
Vascular spasm and degenerative spinal cord lesion	1	1		1	
Vascular spasm and spina bifida	1	1		1	
Vascular spasm and recurrent lymphoangitis, ulceration and epidermophytosis	1	1	1		
	14	24	22	2	0
B Obliterative Vascular Disease and Vascular Spasm					
Thromboangitis obliterans	30	52	22	27	3
Arteriosclerosis with gangrene	4	6	2	4	0
Frostbite with gangrene	1	2	0	1	1
Gunshot wound of femoral artery	1	1	0	0	1
	36	61	24	32	5
Grand totals	50	85	46	34	5

* Sympathectomized by the extraperitoneal operation illustrated in figure 12. They are divided into two groups according to whether obliterative vascular disease was present

different methods of treatment in similar cases. The value of sympathectomy is emphasized, and the relation of the end result to pulsation in the main vessels is brought out.²³

TABLE 7—*Thromboangitis Obliterans Incidence of Major Amputations After Various Forms of Treatment**

	No of Extrem- ities	No of Amputa- tions	Minor Amputa- tions	Percentage of Major Amputations
Consecutive cases before introduction of nerve block with minor amputation when necessary	31	23	7	74.2
Consecutive cases of nerve block and minor amputation when necessary	26	8	14	30.8
Consecutive cases of nerve block, and minor amputations when necessary and sympathectomy	20	3	14	15.0

* This table is presented to show the improvement in the end results of the treatment of thromboangitis obliterans as measured by the incidence of major amputations. The value of the addition of nerve block and sympathectomy to minor amputation (toes) and other conservative measures (cessation of smoking, careful foot hygiene, active and passive vascular exercises) is brought out.

TABLE 8—*Thromboangitis Obliterans Relation Between Pulsation of the Main Vessels and Amputation**

Diagnosis	No of Extrem- ities	No of Major Amputa- tions	Percentage of Major Amputations
(A) Popliteal pulsation present, consecutive cases of nerve block and minor amputation when necessary	16	4	25.0
(B) Consecutive cases of nerve block, minor amputations when necessary and sympathectomy	27	0	0
(A) Popliteal pulsation absent consecutive cases of nerve block and minor amputation when necessary	17	8	47.1
(B) Consecutive cases of nerve block, minor amputation when necessary and sympathectomy	23	3	13.0

* Cases of nerve block without sympathectomy are contrasted with cases in which both procedures were used. They are subdivided according to the presence or absence of popliteal pulsation in order to compare similar cases as far as possible. The addition of sympathectomy appears to have been helpful in reducing the incidence of major amputations.

TABLE 9—*Thromboangitis Obliterans Results of Treatment of Fifty Consecutive Extremities by Sympathectomy in Addition to Other Forms of Treatment**

Patency of Main Vessels	No of Extrem- ities	Nerve Block Necessary	Amputation Unneces- sary	Minor Amputation Necessary	Major Amputation Necessary
All patent	8	0	8	0	0
Either or both dorsalis pedis and posterior tibial obliterated (popliteal present)	19	5	16	3	0
Popliteal obliterated	21	14	8	11	2
Femoral obliterated	2	1	1	0	1
Totals	50	20	33	14	3 (6%)

* In all instances sympathectomy was performed, with other surgical measures as indicated. The incidence of major amputations was 6 per cent. These came in the group with the most advanced degree of main vessel obliteration. Compare with table 7 before the advent of peripheral nerve block and sympathectomy.

²³ Smithwick, R. H., and White, J. C. Peripheral Nerve Block in Obliterative Vascular Disease of the Lower Extremity, Surg., Gynec. & Obst. 60:1106, 1935.

SUMMARY AND CONCLUSIONS

Sympathectomy yields its most satisfactory clinical results when it is performed in such a way that the area is completely denervated by a preganglionic procedure. It is important also that the operation be performed in such a manner as to guard against regeneration.

The most brilliant results are obtained in cases of purely vasospastic disorders. However, worth while improvement may often follow if sympathectomy is performed when both obliteration and spasm of arteries are known to exist.

Various methods of testing for vasospasm are discussed. The value of studying reflex vascular and sweat gland activity is emphasized, particularly with regard to determining both the completeness and the permanence of the results of any operative procedure. The importance of clinical observation and judgment based on experience is mentioned in connection with the selection of cases for operation.

Various changes which take place after sympathectomy are considered in some detail. The difference between complete and incomplete sympathectomy is brought out. The question of "relapse" due to partial regeneration of sympathetic pathways is discussed with particular reference to reflex vascular and sweat gland activity.

The operative technic which has been found to produce the most satisfactory denervation of both upper and lower extremities is described briefly.

Clinical results in cases of both primary and secondary vasospastic disorders are tabulated. The results of various surgical measures utilized in the management of patients with thromboangitis obliterans are discussed in terms of incidence of major amputations.

HEPARIN IN SURGICAL TREATMENT OF BLOOD VESSELS

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TORONTO, CANADA

The valiant efforts made by many investigators to advance the treatment of diseases and injuries of blood vessels have been hampered by thrombosis and clotting in these structures. The uncontrollable factor leading to failure in many cases is not the giving way or leaking of suture lines or weakness, dilatation or stenosis of blood vessels but is occlusion of the vessels by thrombosis. The discovery of the anti-coagulant heparin by Howell¹ in 1916 was therefore an epoch-making event. More recently, experiments by Murray and his co-workers² demonstrating that heparin would also prevent thrombosis were of importance in developing this subject. The final purification of heparin by Best and by Charles and Scott³ made it safe to give this substance to clinical patients.

EXPERIMENTAL DATA

Heparin is a strong organic acid, probably a mucicetin trisulfuric acid. In addition to preventing clotting, it has an important effect on the platelets, preventing their clumping and thereby preventing thrombosis. Its mode of action in this respect is not understood at present. Heparin is obtained from various animal tissues, the lung giving the highest yield for purposes of mass production.

Toxicity—The earlier preparations of heparin contained large quantities of impure material which made them too toxic for clinical administration. With further purification, however, these impurities have been eliminated, and now, with the availability of the crystalline barium salt, the toxic effects have disappeared. Within the last few months some lots of heparin appearing on the market have shown some of the

From the Toronto General Hospital

1 Howell, W. H. Two New Factors in Blood Coagulation—Heparin and Proantithrombin, *Am J Physiol* **47** 328, 1918

2 Murray, D. W. G., Jazues, L. B., Perrett, T. S., and Best, C. H. Heparin and Thrombosis of Veins Following Injury, *Surgery* **2** 163, 1937

3 Charles, A. F., and Scott, D. A. The Preparation of Heparin from Beef Lung, *Tr Roy Soc Canada (Sect 5)* **28** 55, 1934, Studies on Heparin. I The Preparation of Heparin, *J Biol Chem* **102** 425, 1933, The Purification of Heparin, *ibid* **102** 437, 1933

toxic effects which were observed in the earlier preparations, however, more recently these impurities appear to have been removed, and the substance is now nontoxic

Effect of Injection of Heparin—Within a very short time after an adequate intravenous dose of heparin is given the clotting time rises rapidly, the level depending on the dose. If a single dose is given, the clotting time begins to fall within a short time, and from then on it descends rapidly until a normal level is reached (within an hour or two). If after the initial dose the injection is continued intravenously the clotting time can be maintained at any desired level. When administration of heparin is stopped and the clotting time returns to normal, there are no ill effects, and the blood appears to be normal in all respects.

Methods of Administration—It was found that heparin could be administered in various ways. Local application was not particularly effective. Subcutaneous and intramuscular injections were only moderately effective. The best method, which has been used most generally in this experimental and clinical work, is continuous intravenous injection in dextrose solution or physiologic solution of sodium chloride. The injection must be made at such a rate that the clotting time is maintained at a predetermined level, usually two or three times the normal.

When operation or repair of single blood vessels is undertaken heparin may be injected through a needle with a pump just proximal to the areas of repair. The blood stream passing over these areas will have an increased clotting time, which is not evident in the remainder of the vascular system.

Effect of Heparin in Prevention of Thrombosis—The earlier work of Howell demonstrated the ability of heparin to prevent clotting of blood, but there was some doubt at this time whether it would prevent thrombosis. To investigate this problem, superficial veins in the extremities of animals were damaged. On mechanical and chemical irritation of segments of these vessels, occlusion took place in a high percentage. When under similar conditions heparin was given, occlusion did not take place. From several hundred experiments it appeared that heparin was effective when adequate concentrations were maintained in the blood stream.

Arterial Anastomosis—End to end suture of arteries has been carried out successfully by many workers, and by the unprecedented technic of Carrel success has been obtained in a high percentage of cases. My associates and I carried out a fair number of anastomoses with success, and the vessels remained patent when an extremely careful technic was followed. With less care in the operation a large percentage became occluded again, by a thrombus at the suture line. When

smaller vessels such as the brachial and femoral arteries, were sutured, practically all of them became occluded with thrombus. Of over 50 experiments in which heparin was used, the arteries remained patent in more than 80 per cent, as compared with 35 per cent for the controls. In a similar group, with improved technic in administering heparin, all the vessels remained patent. If administration of heparin was continued for seventy-two hours or more, the vessels remained patent. The intima was healed completely, without signs of stenosis or bulging. Specimens recovered many months afterward showed only a slight scar at the site of anastomosis (fig 1).

At this stage my interest was aroused in the healing of the suture lines. Figure 2 shows the stages of repair at different intervals after operation (fig 2).

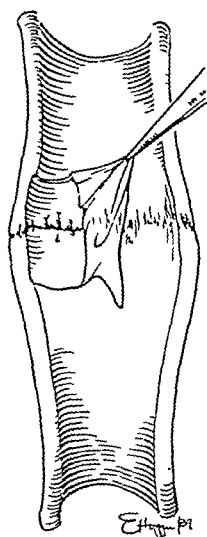


Fig 1—End to end anastomosis of an artery, showing healing of the suture line

Venous Grafts—Venous grafts have been suggested and have been tried by various workers, but I have been unable to find reports of cases in which they were used successfully, either experimentally or clinically. It was thought that, with thrombosis in 100 per cent of control venous grafts, this would be an excellent test of the effect of either regional or general heparinization. Segments of carotid arteries were excised, and a similar length of external jugular vein was removed and anastomosed at both ends to take the place of the artery. The suture material was fine silk. The operations were done quickly and without the extreme care used in Carrel's technic (fig 3).

There was some doubt in the earlier stages whether the thin-walled vein would withstand the high arterial pressure. Under this pressure the venous grafts ballooned out in a sausage shape, and the wall when

stretched was so thin that eddies of circulating blood could be seen through it. The anastomosis in these cases was carried out with a single suture line, as it was found by repeated experiments that reinforcement with stitches or other materials was unnecessary. The whole question of success or failure depended on whether thrombosis occurred at the suture lines and not on the giving way of the wall of the vessel. It was found during the experiments that it was better to make the venous



Fig 2—*A*, end to end suture of an artery, showing absence of healing twenty-four hours after the operation. *B*, end to end suture of an artery, showing perfect healing forty-two days after the operation. The silk suture used in the anastomosis is shown in cross section.

graft considerably longer than the segments of artery removed, so that flexion of the animal's neck would not tear the suture lines. In all the control experiments the grafts became occluded in a short time with blood clot. When heparin was given and its administration continued for not less than seven days, the grafts remained patent. There was con-

siderable difficulty in continuing heparinization for this length of time without interruption and without complication, such as pneumonia, infection of the wounds or disconnection of the apparatus. Over 50 such grafts have been made, and many of these have been exposed surgically at intervals of three months. When the operation was completed successfully and the heparinization carried out without interruption, the grafts remained patent. Several of these grafts have been opened at the time of operation and pieces removed from the wall to study the changes in the venous wall under the change in environment. It was interesting to find that the wall of the venous graft was considerably thicker and more opaque than when it was inserted. If the original venous graft was much larger than the adjacent segments of the artery, the size of the lumen changed during the succeeding few

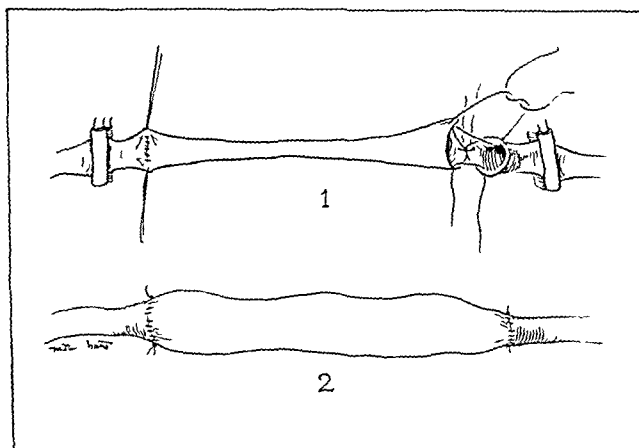


Fig 3—Technic of applying a venous graft

months, diminishing considerably, so that it more nearly approximated the size of the artery. After a few months the wall of the graft was of about the same thickness and had about the same translucence as the adjacent wall of the artery. The surface had the appearance of a thick, fibrous structure with multiple small bleeding points, such as are seen in an ordinary scar. It was adherent to all the structures surrounding it but could be separated with ease. The wall was tough, and on no occasion was it torn during the dissection. There was no evidence of degeneration of the wall in the form of calcareous plaques or bulging. The vessels conducted the blood stream and pulsated normally, as did the adjacent arteries. The wall was elastic and compressible like the wall of an artery. Figure 4 shows a specimen removed after forty-two days. The changes described, such as the increased thickness of the wall, the healing of the suture line and the diminution of the lumen, are apparent. The intima appears normal, with no evidence of degeneration.

Embolectomy—Since the first successful embolectomy, performed in 1911 by Key,⁴ efforts have been made to apply this method of treatment to peripheral arterial embolisms. Failure in many cases has resulted from thrombosis at the site of operation or at the site at which the embolus was lodged. The recent application of passive vascular exercises by Reid and Heermann has saved a great many extremities from gangrene, but it is felt that in many cases if the embolus had been removed early and the circulation restored, the ideal would have been attained. Experiments on the blood vessels of dogs were carried out to investigate the possibilities of embolectomy combined with the use of heparin.

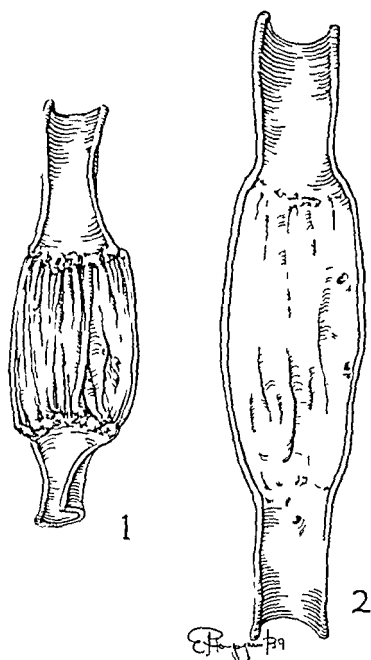


Fig 4—Venous grafts removed (1) eight hours and (2) forty-two days after the operation. Note the difference in the texture and in the lumens of the grafts.

Peripheral vessels in dogs were plugged with foreign bodies and blood clot and were closed. The plugs were removed after periods varying up to three days. Figure 5 shows a section of a vessel at six hours compared with a section of a vessel at forty-eight hours after such an embolus had been placed in the lumen. In the earlier hours the plug is quite free from the intima and can be removed without difficulty, whereas later there is a great deal of reaction in the intima, invasion by leukocytes and adherence of the embolus to the wall. At this stage the plug can be removed only by scraping it off the surface. After

4 Key, E. Ueber Embolectomie als Behandlungsmethode bei embolischen Zirkulationsstörungen der Extremitäten, *Acta chir Scandnav* 54 341, 1921

removal of such an embolus after forty-eight hours, the vessel became occluded again within a few hours. If, however, the animal was successfully heparinized for several days, the vessel remained patent and the intima healed over. Specimens removed a month later showed the artery to be clear of thrombus and to be carrying on the circulation

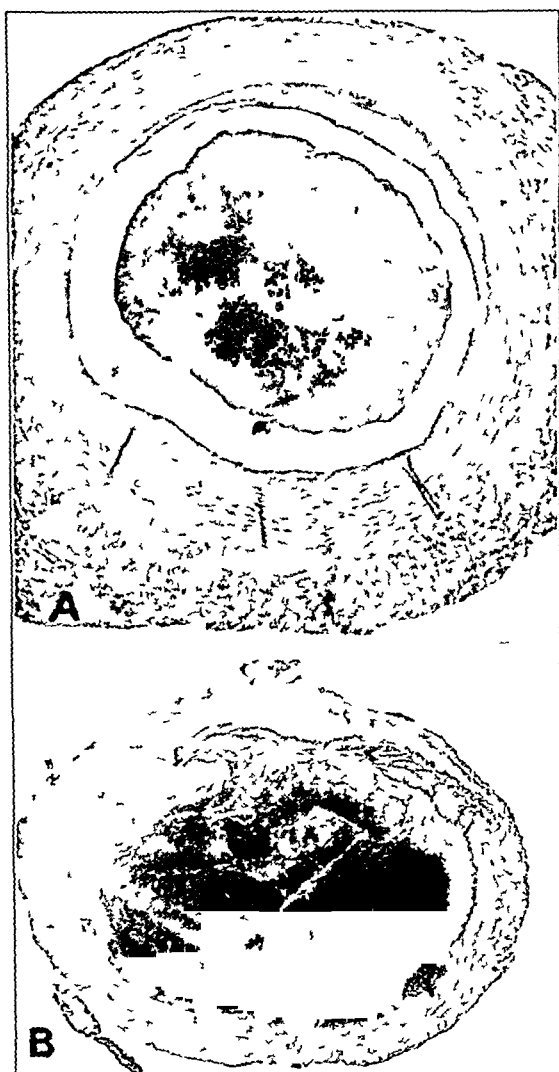


Fig 5—*A*, cross section of an arterial embolus of six hours' duration. The embolus is free from the wall of the vessel. *B*, inflammatory reaction produced in the wall of the vessel by an embolus which has been in place for forty-eight hours.

normally. This gave encouraging evidence that embolectomy in human patients might be carried out more successfully than formerly if heparin were used.

Effect of Heparin on Portal Thrombosis—The knowledge that splenectomy in human beings has frequently been complicated by portal and systemic thrombosis encouraged my associates and me to perform some experiments to see whether heparin would be as effective in the portal system as in the systemic. In a group of animals the spleen was removed and the splenic vein injured. In all the controls the splenic vein became thrombosed, when, however, heparin was given successfully for seven days or more, the splenic veins remained patent in 90 per cent of cases. This also was encouraging evidence that heparin might be used to advantage in operations involving the vessels of the portal system.

Transplantation of Organs—Many successful experimental transplantations of organs have been carried out. In our hands, however, there was a high percentage of failures. With such operations as transplantation of the kidney in animals, the circulation was maintained in relatively few instances. If, however, heparin was given after the operation and its administration continued for several days, the vessels remained patent and the end results were much more satisfactory.

Further evidence of the effectiveness of heparin in preventing thrombosis was provided by repeating Shionoya's⁵ experiments of placing a transparent tube as a shunt between the arterial and the venous system. Under ordinary conditions this tube filled rapidly with thrombus. When, however, heparin was given in sufficient concentration, the tube remained clear.

Coronary Occlusion—By irritating the coronary arteries of animals with sclerosing solutions, Best and Solandt⁶ showed that thrombosis occurred in a high percentage of cases. When, however, heparin was given, this could be prevented. They found also that the mural thrombus forming with relation to the infarcted area in the chambers of the heart did not occur when heparin was used.

CLINICAL DATA

Experimental work on heparin was undertaken in the hope that this substance might eventually be used clinically for diseases in which thrombosis in blood vessels presents an unsolved problem. Thrombosis occurs spontaneously in a large group of cases of diseases of the venous and arterial systems. Such diseases are followed not infrequently by such complications as embolism, resulting in devitalization of tissue and in some cases progressing to gangrene. Pulmonary embolism is

5 Shionoya, A. T. Studies in Experimental Extracorporeal Thrombosis. Effects of Certain Anticoagulants (Heparin, Hirudin) on Extracorporeal Thrombosis and on the Mechanism of Thrombus Formation, *J. Exper. Med.* 46: 19, 1927.

6 Solandt, D. Y., and Best, C. H. Heparin and Coronary Thrombosis in Experimental Animals, *Lancet* 2: 130, 1938.

one of the dreaded complications, resulting in some cases in sudden death and in others in prolonged illness with persistent disability. In another group of cases, thrombosis may destroy the results of surgical treatment of aneurysms, removal of important vessels for invasion by tumor or ligation of important vessels, such as the common and the internal carotid artery.

With experimental evidence to prove that heparin would prevent thrombosis, my associates and I began giving it to patients. Former attempts by Mason,⁷ McClure and others to use heparin for blood transfusions showed that it was too toxic to be of practical use. However, with the purified form of heparin available, we determined to make an attempt to use it clinically. In the first case, regional heparinization through the brachial artery was carried out successfully. After this other patients were given heparin intravenously, but toxic effects were observed with the 250 unit material. With further purification by Charles and Scott, the crystalline barium salt was obtained, and this was found to be nontoxic. The dose was increased until, on several occasions, a clotting time of one and one-half hours was reached without ill effects. To several patients heparin has been administered at intervals of several months without signs of anaphylaxis.

Arterial Suture—The usual surgical practice when a large vessel is bleeding is to apply a ligature. In most circumstances this is all that is necessary, and recovery is prompt. There are cases, however, in which it is more desirable to restore the circulation if possible. With the use of heparin, operations for repair of holes in vessels or for end to end anastomosis may be quite successful, as is shown by the following group of cases. The first case will be reported in detail, the others, in summary.

REPORT OF CASES

A patient's arm in the region of the elbow was severely crushed in a motor accident. Within a few hours the hand was cold, dark blue, insensitive (with no pulsations at the wrist) and greatly swollen in the antecubital fossa. It was obvious that the lower end of the brachial artery had been severely injured. At operation it was discovered that the brachial artery about $1\frac{1}{2}$ inches (3.2 cm) above its bifurcation was torn across completely and the ends separated for a distance of $1\frac{1}{2}$ inches. Both ends were plugged with clot. This clot was cleared out, and the ragged ends were trimmed off until a sound segment of wall was reached. With three stay sutures in place, an end to end anastomosis was carried out with a continuous suture of silk. Heparin was injected into the vessel at this time, and a continuous intravenous injection of heparin was carried on for five days more. The vessel functioned normally and has continued to do so for one and one-half years. The patient is back at his work as a garage mechanic, and the arm is normal in all respects. This was the type of case in which ordinarily, if operation were decided on, the ends of the vessel would have been tied. From

⁷ Mason, E. C. Note on the Use of Heparin in Blood Transfusion, *J. Lab. & Clin. Med.* **10**: 203, 1924.

the amount of injury and crushing of the brachialis anticus muscle and other structures, including the collateral vessels in front of the elbow, it is more than probable that gangrene would have supervened in the hand if the vessel had not been repaired

The extensive collateral circulation in cases of arteriovenous aneurysm allows radical ligation of the main vessels involved and excision of the aneurysm if desired. With the use of heparin, however, reconstruction of vessels can be carried out successfully if it seems to have any advantage over other methods of treatment. We have operated in 3 such cases, and in all of these the vessels were reconstructed with a satisfactory result.

In 1 case a bullet passing through Scarpa's triangle had produced two arteriovenous aneurysms between the superficial and deep femoral arteries and then corresponding veins. The aneurysms were removed and the vessels reconstructed, and heparin was administered intravenously. The circulation in the extremity has remained normal since that time. Two arteriovenous aneurysms (one in the axilla and the other in the groin) have been operated on and the vessels repaired successfully, with a return to normal of the circulation of the extremities.

In another case, during an operation for partial thyroidectomy by an excellent surgeon the common carotid artery on the right side was divided across just below its bifurcation. In this case also the accepted treatment would have been to tie both ends of the carotid artery. Although this would have been successful in most such cases, there is the danger that in about 25 per cent the patient would have cerebral symptoms, with hemiplegia in some instances and death in others. Under these circumstances it was highly desirable to repair the vessel if possible to eliminate these dangers.

After the vessel had been trimmed of its damaged portions, there was considerable difficulty in bringing the ends into apposition. However, by flexion, lateral bending and rotation of the neck this was accomplished. With three stay sutures in place, the anastomosis was carried out with a continuous line of silk suture. Heparin was injected at the site of anastomosis, and injection was continued intravenously for several days. Immediately after removal of the arterial clips, the circulation was restored. The patient's head and neck were supported in a plaster cast to prevent stretching at the site of the anastomosis. There was no evidence of any peripheral or central impairment from the accident or from the operation for repair of the vessel and the patient recovered.

Venous Grafts—When accidents or pathologic lesions destroy segments of major arterial trunks, the usual procedure is to ligate the vessels involved. The disastrous results sometimes following such procedures have led surgeons to attempt end to end sutures of the vessel

involved, and cases have been recorded in which successful results were obtained. In a large percentage, however, the operation has failed because of thrombosis occurring at the involved area. In important vessels, such as the internal carotid artery, the aorta and the major trunks to the extremities, disaster sometimes follows obliteration of the vascular trunks. The results of experiments with suture of arteries and the use of venous grafts were so satisfactory that it was hoped that these principles might be applied to human beings. After a successful experience in 1 case, my associates and I propose, in suitable cases, to repair vessels with venous grafts when they cannot be sutured end to end.

The clinical case in which our experience of venous grafting was obtained was one of popliteal aneurysm. The swelling was enlarging rapidly and gave the impression that it would burst. The leg was paralyzed, there was a great deal of pain, and the circulation below the knee was impaired. The pulses at the ankle were weak compared with those on the opposite side.

On removal of the aneurysmal sac at operation a gap of $3\frac{1}{4}$ inches (8.2 cm) was left between the ends of the popliteal artery. The artery was degenerated and dilated, and the wall was thickened. These changes were much more marked in the proximal than in the distal segment. It was appreciated that the collateral circulation would probably be sufficient to prevent gangrene of the foot, but the high incidence of gangrene following ligation of the popliteal artery was also considered. As this seemed a suitable case in which to attempt a venous graft, the external jugular vein on the right side was removed. This specimen was considerably smaller than the artery, and it was appreciated that it was not an especially suitable graft in this particular case. Anastomosis was carried out between the venous graft and the segments of the artery. There was a great disparity in size between the artery and the graft, and it was necessary to stretch the graft greatly to complete the anastomosis. It was feared that the stretching necessary to make the vein reach the size of the artery would damage its wall. Moreover, the aneurysm had excavated the tissues on the popliteal surface of the femur, so that the graft on this surface was stretching across an open space which ultimately would become filled with blood clot. On its superficial aspect, viable tissues were closed to give it support. Heparin was injected into the segments of the artery and the graft, and the clips on the artery were removed. Immediately the circulation returned to the foot, and there was distinct and forcible pulsation in the vessels at the ankle. The graft when fully distended was less than half the size of the adjacent segments of the artery. However, the circulation was carried on quite satisfactorily through it. The patient was given heparin intravenously to keep the clotting time at a level of about fifteen minutes for two weeks (fig. 6).

The circulation remained normal in the foot for two and a half weeks after operation. At this time the patient rather suddenly noticed a recurrence of pain in the popliteal space. With a stethoscope a bruit could be heard distinctly, and the pulsation of the vessels in the foot was less distinct than formerly. It was obvious that another aneurysm had occurred. The popliteal space was again explored. There was a large false aneurysm, the walls of which were removed. The venous graft and segments of the artery were exposed. These were normal in every respect, and the circulation was being carried on. The wall of the venous

graft was thicker than at the original operation, and it showed the changes which our experience with animals had led us to expect. The only defect was at an area about $\frac{1}{4}$ inch (0.6 cm) distal to the proximal suture line. Here the wall of the venous graft on its anterior surface had bulged, forming a small aneurysm about $\frac{5}{8}$ inch (1.8 cm) in diameter. At one point this small aneurysm had given way, and through this opening it communicated with the false aneurysm. When this opening was occluded and the circulation allowed to return, there was normal pulsation in the vessels of the foot, and the pulse could be demonstrated in the venous graft and in both segments of the artery. With clips on the segments of the artery, a probe could be passed through the opening in the aneurysm and through both suture lines, there was no obstruction or stenosis. (From the

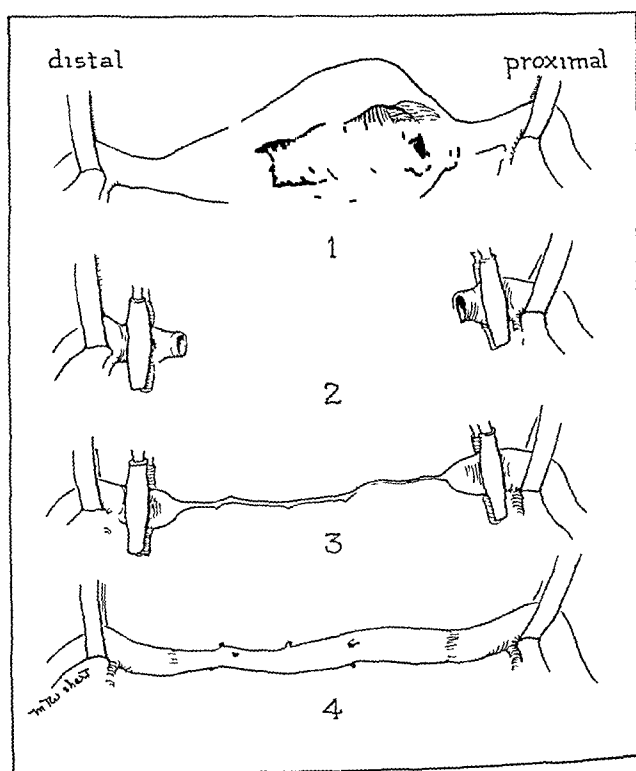


Fig 6—Stages of resection of an aneurysm and application of a venous graft in the popliteal artery in a clinical case

evidence found at operation it was obvious that the venous graft had given way at a point at which it had been overstretched. On another occasion a larger vein, matching the size of the artery more accurately, will be used.)

We were in doubt whether the graft should be excised and the arteries ligated. It was decided, however, to repair the aneurysm. Flaps were cut in such a fashion that the lumen of the vessel was maintained and the aneurysm repaired. When circulation was restored after this, there was excellent pulsation in the graft and in the distal segment of the artery, although this was less forcible than before. The

patient was again heparinized. The circulation in the foot remained normal, and at the time of writing, fourteen months after the operation, the patient is able to do light work.

This was a most instructive case, as it demonstrated the possibility of using a venous graft to bridge a gap in an artery in a human being. It showed that the graft survives when the patient is treated with heparin, that its wall becomes thickened and that stenosis does not occur at the suture lines. The failure of a small area of the graft was probably due to the overstretching which was necessary to make the vein fit the artery.

Even if such a graft functioned for only a few days it might overcome the dangers resulting from acute failure of circulation, under many conditions. There is evidence, however, that the graft may survive and function indefinitely.

Mesenteric Thrombosis—Whatever the underlying cause of mesenteric thrombosis may be, the most important pathologic change associated with the disease is thrombosis of mesenteric vessels. As this continues to spread even after resection, the mortality rate for this disease is high. It appeared, therefore, on the experimental evidence, that heparin might be of value in preventing the spread of thrombosis in this disease. In 6 cases in which there was gangrene requiring resection of from 18 inches (45 cm) to 7 feet (2 meters) of bowel, heparin was given immediately after the operation. According to the experience of the surgeons operating in these cases, none of the patients would have survived. It is interesting, therefore, to report that the first 4 are still alive and well more than a year after their operations. In the case of the fifth the diagnosis was made late in the course of the disease. The patient died twenty-four hours after resection of the bowel. At post-mortem examination there was no extension of gangrene, and the peritoneal cavity was normal, the patient had died of bilateral bronchopneumonia. In the sixth case, 7 feet (2 meters) of the terminal portion of the ileum, the cecum and the ascending colon was resected because of extensive gangrene with grayish, sloughing, foul-smelling bowel with peritonitis already in a fairly advanced stage. The patient lived nine days, at postmortem examination there was no extension of the gangrene in the bowel, and, although the patient died of peritonitis, it was the pathologist's opinion that the condition had persisted from the serious peritoneal infection which was present at the first operation.

Considering the high mortality from this disease, it probably is a significant fact that the first 4 patients of this series recovered without complications and are still alive and well. The next 2 died of late complications of the disease and not of extension of thrombosis in the mesenteric vessels. This evidence would indicate that when there is sufficient gangrene of the bowel to require surgical resection in cases of mesenteric thrombosis it would be a great advantage to use heparin.

immediately after the operation. My associates and I continue injection of heparin for periods varying from ten days to two weeks keeping the clotting time of the blood between fifteen and twenty minutes.

Splenectomy—With experimental and clinical evidence that heparin is effective in the portal system, it was thought that it might be used to prevent portal and systemic thrombosis following splenectomy. In certain diseases (such as familial jaundice) for which splenectomy is done, the mortality rate is high because of portal thrombosis. We have given heparin postoperatively to a group of 8 splenectomized patients. While this group is too small from which to draw conclusions it was interesting to note that in none did thrombosis develop in any form. From our knowledge of the effect of heparin in preventing thrombosis it would seem advisable to give heparin postoperatively to splenectomized patients in whom thrombosis is likely to occur.

Blood Transfusions—A large number of blood transfusions have been done with the use of heparin as an anticoagulant. It has been given to the donor so that the blood may be drawn without clotting. In some cases the heparin has been added to the drawn blood. If the blood is to be given immediately to the recipient from 1 to $1\frac{1}{2}$ units of heparin per cubic centimeter of drawn blood is sufficient. The small amount necessary is inexpensive compared with some of the other anticoagulants in use.

Embolectomy—Clinical experience has shown that unless an embolus is removed from a peripheral artery within ten or twelve hours the prognosis is not good. The results of this operation are increasingly bad with further lapse of time. Moreover, even in the earlier phases failures are due frequently to a thrombus obliterating the vessel either at the operative site or where the embolus is lodged. The weakened condition of the patient with chronic heart disease, high venous pressure or low blood pressure contributes to the formation of a thrombus. It was thought, therefore, that heparin might be of great value in this operation.

Twelve arterial embolectomies have been done and heparin used postoperatively. In all cases this procedure was successful if the lumen was cleared completely and the circulation restored. Heparin was injected into the vessel at the site of operation and the injection was continued intravenously for from three to fourteen days. In all 12 cases the vessels remained patent, and the circulation has been maintained in the extremities.

Two of the patients died at different intervals after the operation. In 1 case autopsy enabled us to prove that restoration of the circulation had taken place. This patient had been operated on twenty-five hours after the first appearance of symptoms of embolism involving both the common iliac and the femoral arteries. The emboli were removed with moderate difficulty, as they tended to stick to the intima of the vessel.

Heparin was injected locally, and when the clips were removed the circulation returned quickly to both feet. The clotting time of the blood was kept at twenty minutes for two weeks, then heparin was discontinued. The circulation remained normal in the feet, and the patient made an excellent recovery. The patient died later of other lesions. The aorta and the vessels going to the legs were recovered. These were all perfectly clear, with no sign of thrombosis or clots either at the operative site or in the areas where the emboli had lodged. The incision through which the emboli were removed was perfectly healed. A photomicrograph of the tissue through which the incision had been made showed the intima to be healed perfectly, with no sign of thrombosis or clotting. In the other case in which the patient died twenty-four hours

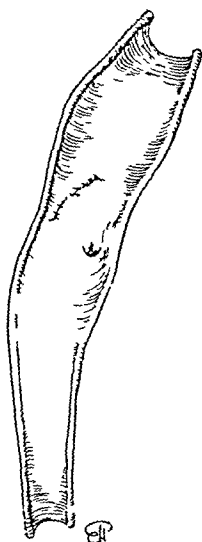


Fig 7—Common, superficial and deep femoral arteries removed twenty-four hours after embolectomy in a clinical case. The suture line is firm and smooth, with no sign of thrombosis or clot.

after the operation, the vessels were quite clear, with no sign of thrombosis or blood clots. The suture line was intact (fig 7).

Although in most cases of peripheral embolism blockage is incomplete and in others there is sufficient collateral circulation, gangrene of the extremities often develops, necessitating amputation. Many patients respond to treatment with the pavaex machine, but in my experience this device will not prevent gangrene in all cases. It is suggested, therefore, that if operation is done within the first twenty-four hours and combined with the use of heparin better results may be expected.

Phlebitis—Although phlebitis is considered by some to be a "medical disease," its incidence as a postoperative complication only too often brings it to the surgeon's notice. The striking improvement of the

symptoms of this disease under treatment with heparin probably warrants a short discussion of the subject. Unquestionably there is a considerable difference in cases of thrombophlebitis. Thrombi occurring in varicose veins probably have a different origin from those observed in cases of phlegmasia alba dolens. It was with extreme interest therefore, that my associates and I watched the course of patients with this disease. It was observed that the earlier heparin was administered after the beginning of an attack of phlebitis, the more effective was the treatment. Although there is great variation in the course in different cases of thrombophlebitis, we were impressed by the fact that the recovery was more rapid and more complete in patients treated with heparin than in a group of controls. Within a few hours, the symptoms were much improved, pain was diminishing or had disappeared and the temperature had begun to fall and within a few days had returned to normal. The edema began to recede within one or two days and frequently disappeared completely within a week or ten days. Although it is too early to judge the end results, there has been less persisting edema than in the control group. Pulmonary embolism, the common complication occurring in 15 per cent of 300 cases, did not occur in 81 cases in which heparin was used. In 5 cases of migrating thrombophlebitis the symptoms disappeared more slowly than in cases of the more acute forms of the disease. In 3 of these cases there were recurrences of the disease within a few months.

It is uncertain why heparin should produce these effects on thrombophlebitis. The only effect that heparin could have is to prevent extension of thrombosis. It is possible, therefore, that the healing of the lesion already present is allowed to take place and that with prevention of extension of the process the active inflammation recedes and the symptoms disappear with it.

The treatment in these cases was carried out as in the others by a continuous intravenous injection, the clotting time of the blood being kept between fifteen and twenty minutes. After the first three or four days, when the acute symptoms had disappeared, the patient was encouraged to exercise actively in bed, and within an average of one week of the beginning of treatment the patient was encouraged to sit out of bed and do active leg exercises with weight bearing. The injection was continued during this period. If no untoward signs or symptoms developed by the second or third day he was out of bed, the injection was discontinued and the patient was discharged from the hospital. Most of the patients in this group of 81 cases were discharged within six to fourteen days of the beginning of treatment for acute thrombophlebitis. Except in the cases of migrating thrombophlebitis, there has not been a recurrence of the disease in two and one-half years.

Considering the great variation in different cases of thrombophlebitis, it might be expected that many of our patients would have recovered in a

short time without heparin treatment. However, we were greatly impressed by the seriousness of the disease in many of the cases, and it was amazing to see the patients recovering and out of bed in such short periods. Whether heparin had a specific effect is difficult to determine, but these patients have returned to normal activity in a considerably shorter time than the average for a (larger) group of control cases.

Thrombophlebitis and Pulmonary Embolism—Encouraged by the spectacular results in patients with thrombophlebitis, we decided to try heparin for a group of patients with pulmonary embolism. It was realized that when pulmonary embolism develops large areas of the peripheral venous system may still contain thrombi, which may be discharged to repeat the accident at any time. As heparin has no effect in dissolving the clot, it cannot affect the thrombi in any way. Because other forms of treatment are so ineffective and Trendelenburg's operation is such a serious one, with relatively few recoveries to date, it was considered worth while to give heparin a trial. Up to the present time, 29 patients with massive pulmonary embolism have been treated with heparin. These patients all presented the usual picture of the disease, with sudden onset, marked collapse and rapid pulse. Several had multiple embolisms with infarcts which were demonstrated on clinical and roentgen examination. Heparin therapy was instituted at intervals of a few hours to several days after the attack. The results were surprisingly good. Of the 29 patients, none have died of embolism, although death seemed imminent for some. The dyspnea and other signs of the disease improved rapidly, and within twenty-four hours all the patients stated that they were improved. From that time on the symptoms rapidly disappeared. With one possible but unproved exception none of the patients had further emboli. With this disease, as with thrombophlebitis, it is impossible to predict the outcome, as it is well known that 80 per cent of patients recover. In this group, however, the involvement in many of the cases was serious, and, judging from our experience with the disease, was of the type for which the prognosis is extremely bad. It is possible that the psychic effect of some active form of treatment was important, but this factor is difficult to evaluate.

The treatment carried out in this group was similar to that in cases of uncomplicated thrombophlebitis. The patients were encouraged to exercise in bed after the third day and were allowed out of bed at periods varying between six days and two weeks.

Two other patients who were treated with heparin died, and post-mortem examinations were made. The first died of general peritonitis following a partial gastrectomy, and thrombophlebitis and pulmonary embolism occurred as postoperative complications. At autopsy the infarcts of the lungs were seen to have been resolving, and there was

no recently formed clot or thrombus either in the pulmonary vessels or in the peripheral venous system. An area in the left common, external iliac and femoral veins, the region of which was obviously the site from which the embolus had come, showed some remaining thrombus, but this was firmly attached to the wall of the vein. In the second case the patient recovered after treatment with heparin and was well for four months. After this obstruction of the small bowel developed as a result of postoperative adhesions. It was discovered also that he had an actively bleeding duodenal ulcer. As this was a positive contraindication to treatment with heparin, the substance was not administered on this occasion. At autopsy in this case it was demonstrated that the patient had died of obstruction of the small bowel. There were scars of the previous embolisms which had healed on treatment with heparin. Recent pulmonary emboli had occurred during the last illness, when it was considered unwise to give him treatment with heparin because of his bleeding ulcer.

While our experience with heparin in cases of pulmonary embolism is limited to this relatively small group of cases, the effect has been so striking that we are encouraged to continue its use in future cases.

Postoperative Heparinization—As pulmonary embolism is one of the commonest postoperative complications, it was decided to treat a group of patients with heparin in an attempt to prevent this. Four hundred and forty patients have been given heparin, the clotting time being increased to between fifteen and twenty minutes. None of these had thrombosis at the site of injection even though the steel needle was left in for periods varying between a week and two weeks. No thrombosis or embolism occurred in any patient who was free from it at the beginning of treatment, and in those who had thrombosis there was no extension of the process. Obviously this is too small a group of cases from which to draw conclusions, but it is significant that cases of many of the conditions in which thrombosis and pulmonary embolism tend to develop were included in this group.

SUMMARY

Heparin was discovered by Howell,¹ who showed it to be an anti-coagulant. Further purification was carried out by Best and by Charles and Scott. Experiments by Murray demonstrated that it would prevent thrombosis.

The purified form of heparin has been shown to be nontoxic to animals. In many operations on veins and arteries it has been shown to prevent thrombosis and clotting until healing has taken place. Venous grafts in arteries have been kept patent by its use and have functioned satisfactorily for one and one-half years.

In 440 patients in the hospital treated with heparin, thrombosis and embolism did not occur. Patients with thrombophlebitis were thought to be improved by the treatment. Striking improvement was observed in a group of patients with pulmonary embolism, with 1 possible but unproved exception, none of these patients had further embolisms, and none died of pulmonary embolism. Embolectomies were successful in 12 cases when heparin was used. In 1 case a venous graft was placed in an artery, this remained patent and functioned satisfactorily. It is suggested that heparin is a most important agent for prevention of thrombosis when operation for repair of blood vessels is undertaken. Heparin might also be used to advantage for diseases in which thrombosis and clotting in the blood vessels occur.

Prof C H Best collaborated with me in this work. Mr L B Jaques, Dr T S Perret, Dr R Wilkinson and Dr R MacKenzie furnished assistance. Financial help was given by grants to these assistants by the Banting Research Foundation. The heparin used in the earlier stages of the work was donated by the Connaught Laboratories. Mr J S McLean provided financially for the supply of heparin used in these experiments during the past year.

INFLUENCE OF TEMPERATURE ON THE DEVELOPMENT OF GANGRENE IN PERIPHERAL VASCULAR DISEASE

NORMAN E. FREEMAN, M.D.

PHILADELPHIA

The fact that heat is brought to the extremities by the flow of blood is generally recognized. The temperature of the part has come to be accepted as indicative of the state of circulation to the tissues. When the hands or feet are cold, it is natural to believe that the blood supply is reduced. Similarly, warmth of the parts indicates adequate blood flow.

It has long been established that the circulation to the extremities is increased by the application of heat and decreased when cold is applied. Quantitative studies¹ have demonstrated the relationship between elevated temperature and increased flow of blood. Since warmth of the extremities is closely related to the circulation and since it is recognized that the blood flow may be increased by the application of heat it is natural to attempt to correct the cold due to inadequate circulation by applying heat.

Patients with impaired circulation often complain of the coldness of their extremities. The pain which is associated with the vascular insufficiency is frequently relieved by keeping the parts warm and is increased when they are cold. Under such circumstances it is probable that the vasoconstriction brought about by the low temperature reduces the circulation. Warmth, which allows the vessels to relax, is followed by an increase in the flow of blood sufficient to supply the needs of the tissues.

From the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania.

1 (a) Hewlett, A. W., and Van Zwaluwenburg, J. G. The Rate of Blood Flow in the Arm, *Heart* **1** 87, 1909. (b) Stewart, G. N. Studies on the Circulation in Man. I. The Measurement of the Blood-Flow in the Hands, *ibid.* **3** 33, 1911. (c) Rein, H. Die Thermo-Stromuhr, *Ztschr. f. Biol.* **87** 394, 1928. (d) Freeman, N. E. The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* **113** 384, 1933. (e) Kunkel, P., and Stead, E. A., Jr. Blood Flow and Vasomotor Reaction in the Foot in Health, in Arteriosclerosis, and in Thromboangitis Obliterans, *Clin. Investigation* **17** 715, 1938.

These needs, however, are dependent on the metabolic rate. It is well known from experiments on cold-blooded animals - that the metabolism is increased by elevating the temperature. It is probable that a similar relationship between metabolism and temperature exists in the tissues of warm-blooded animals. Extremities which are cold, therefore, probably have a low metabolism. Although the vasoconstriction which results from the cold may be relieved by the application of warmth, the tissue metabolism will be increased at the same time. In patients with normal blood vessels the more rapid circulation produced by heat will be able to care for the increased metabolic needs. When

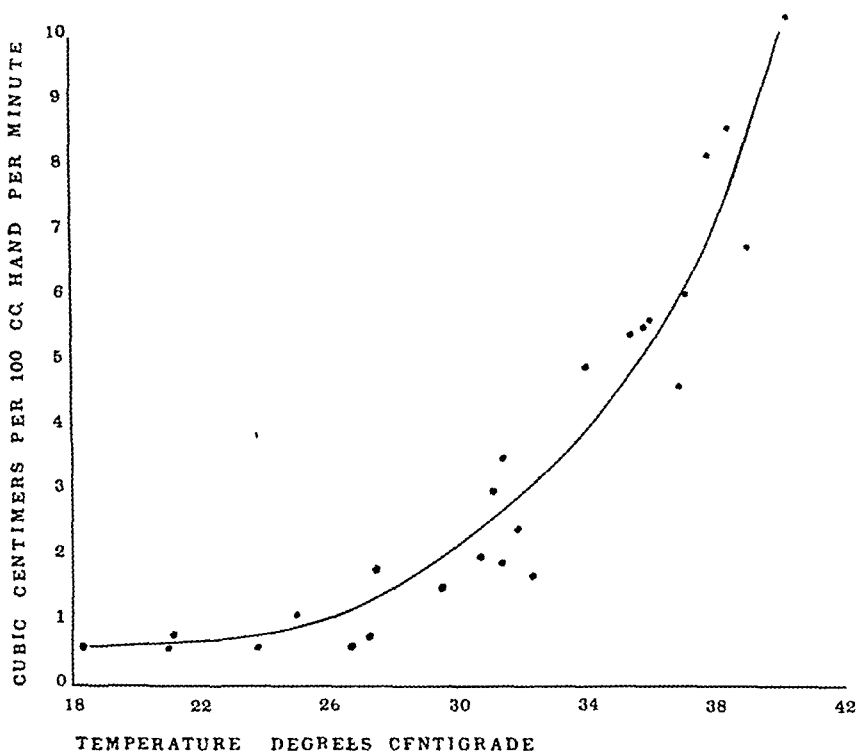


Fig 1—Effect of increasing the temperature of a bath in which the hand was immersed, on the volume flow of blood through the hand. Twenty-five determinations of blood flow were made on the same patient on five successive days.

there is organic occlusion of the blood vessels so that the capacity for dilatation is limited, the circulation may not be able to develop to the extent required by the elevation of tissue metabolism. Under such circumstances the discrepancy between the needs and the blood supply of the tissues may actually be increased by the application of heat. From this standpoint the absolute blood flow is not the criterion of an

adequate circulation. It is the blood flow in relation to the metabolic needs of the tissues which is of significance. A diminished blood supply which is quite adequate for tissues with a low metabolism may be inadequate if the local metabolism is elevated.

Gangrene has been defined as "the dying of tissue due to interference with local nutrition." It is readily understandable that gangrene should result from complete occlusion of the blood supply. Examples of this condition are to be found in peripheral embolism or in major arterial thrombosis associated with Buerger's disease or arteriosclerotic gangrene. The blood supply may also be obstructed by extreme vasoconstriction as in Raynaud's disease. When the occlusion of the arterial supply is partial, the possibility of increase in the blood flow is limited. The

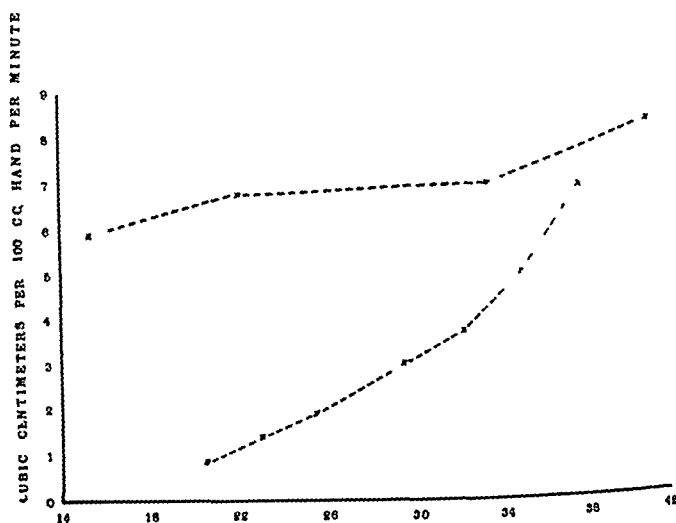


Fig 2—Effect of changes in local temperature on the volume flow of blood through the sympathectomized hand (upper curve) ten days after sympathectomy and through the same hand (lower curve) six months later.

needs of the tissues are then of prime importance and may determine whether or not gangrene will occur. Gangrene, from this standpoint, will occur as the result of a discrepancy between the local demands of the tissues and the supply of blood available to meet these nutritional needs. In a study of the effect of temperature on the production of gangrene it is therefore necessary not only to determine what factors influence the rate of blood flow but also to ascertain the effect which these factors exert on the local metabolism.

The quantitative relationship between blood flow and temperature not only in the normal but also in the sympathectomized hand was investigated in a study previously reported.^{1a} The circulation through the hand was measured by the plethysmographic technic of Hewlett and Van Zwaluwenburg^{1a} with the hand immersed in water at different

temperatures. It was found that as the temperature of the bath in which the hand was immersed was gradually increased there occurred a rise in the rate of blood flow, as shown in figure 1. Immediately after sympathectomy the circulation was stabilized, but six months later the flow was found to vary directly with the temperature. The relationship between blood flow and temperature in the sympathectomized hand is illustrated in figure 2. This observation has been repeatedly confirmed. The absence of regeneration of vasomotor fibers was checked by appropriate tests.

It has long been recognized, since the work of Roy and Brown,³ that the tissues exert an influence on their blood supply in such a way as to increase the circulation in accordance with the metabolic needs. The increase in blood flow through working muscles was recognized by

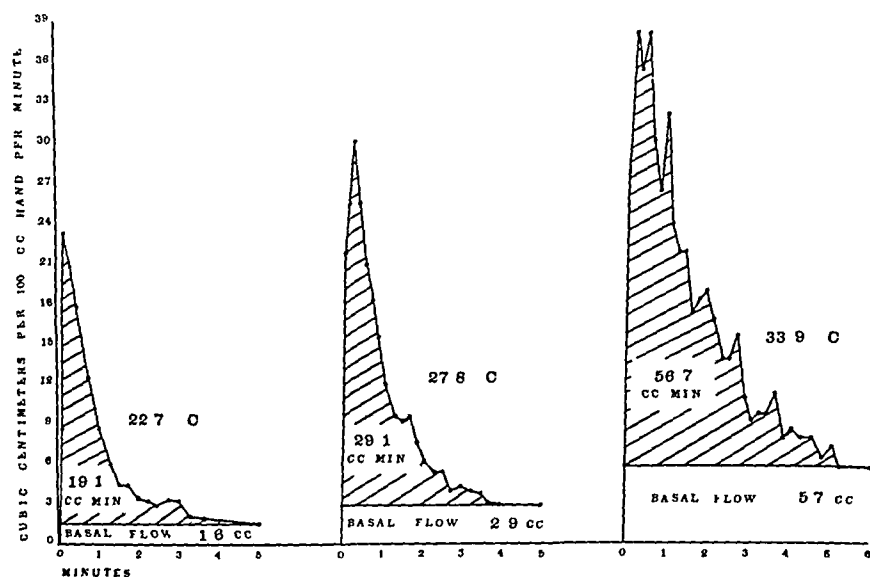


Fig 3—Effect of changes in local temperature on the “reactive hyperemia” which resulted after release of a tourniquet which had occluded the circulation to a sympathectomized hand for ten minutes at each of three temperatures. The excess of blood flow above the basal flow was measured with a planimeter.

Chauveau and Kaufmann⁴ in 1887. If the circulation is temporarily occluded, a marked increase follows release of the tourniquet. This reaction was first described by Cohnheim⁵ in 1872 and was studied

3 Roy, C. S., and Brown, J. G. The Blood-Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, *J. Physiol.* 2: 323, 1879-1880.

4 Chauveau, A., and Kaufmann, M. Experiences pour la détermination du coefficient de l'activité nutritive et respiratoire des muscles en repos et en travail, *Compt. rend. Acad. d. sc.* 104: 1126, 1887.

5 Cohnheim, J. Untersuchungen über die embolischen Prozesse, Berlin, A. Hirschwald, 1872.

by Roy and Brown,³ by Lewis and Grant⁶ and by Montgomery, Moore and McGuinness.⁷ They observed that the extent and the duration of the reactive hyperemia, i. e., the increase in blood flow after release of the occlusion, was dependent on the duration of the circulatory occlusion and on the temperature at which the part was maintained. Lewis and Grant⁶ referred to this phenomenon as a "repayment of a blood flow debt." We studied the quantitative aspects of this reaction in the sympathectomized hand with the temperature stabilized at different levels. It was found in 17 experiments on 5 persons that whether the length of the occlusion was varied from two to twelve minutes, or whether the rate of the blood flow was altered by changing the local temperature, the equivalent of the debt was repaid. Figure 3 illustrates the response in a subject which resulted after occlusion of the circulation for ten minutes at each of three temperatures. The excess blood flow over the basal level was measured, and the total "repayment" was found to approximate the established "debt."

Further studies showed that the observed quantitative relationship held only for short durations of occlusion and at the lower temperatures. When prolonged deprivation was tried, the repayment far exceeded the debt. Pain was produced, especially at the higher temperatures. It seemed as though, with prolonged occlusion, the physiologic nature of the reaction was altered and a pathologic condition was produced. Evidence for this belief was afforded by the appearance of petechial hemorrhages in the skin when the hand was deprived of circulation for five minutes at 40 C (104 F). The inflammatory reaction of tissues in an extremity which has been the site of a major arterial occlusion with vascular insufficiency for an extended period of time illustrates a comparable phenomenon.

These observations gave support to the concept originally advanced by Roy and Brown³ that the vasodilatation was brought about "either by some stimulus acting directly on the walls of the vessels, or indirectly on these through the medium of nutritive changes of the tissue elements." Since a quantitative relationship was observed between temperature, duration of circulatory arrest and subsequent vasodilatation, it seemed likely that the circulation through the sympathectomized hand with the temperature stabilized was modified by the metabolism of the tissues.

Further evidence for the peripheral control of the circulation was sought in determinations of the blood flow through sympathectomized paws of dogs together with analyses of the arterial and venous blood

6 Lewis, T., and Grant, R. Observations upon Reactive Hyperaemia in Man, *Heart* **12** 73, 1925

7 Montgomery, M. L., Moore, J. M., and McGuinness, J. S. Reactive Hyperemia. Relation of Duration of Increased Blood Flow to Length of Circulatory Arrest, *Am J Physiol* **108** 486, 1934

for oxygen and carbon dioxide.⁸ It was found that in any one experiment the circulation varied directly with the temperature, although the difference between the arterial and the venous blood in respect to oxygen and carbon dioxide contents remained constant. With increase in local temperature an increase in local metabolism was therefore demonstrated. The blood flow increased simultaneously to care for the increased needs.

These observations were made in sympathectomized areas, which were free from vasomotor control, and the question may be raised whether they are applicable to tissues which are subject to vasomotor control. The control by the tissues of the quantity of blood supplied to them would appear to be a fundamental property on which the vasomotor regulation was imposed to relate the supply to any tissue to the needs of the body as a whole. Since the increase of circulation with elevation of local temperature was observed in the normal hand, and since the phenomenon of reactive hyperemia was also found in the presence of an intact vasomotor supply, it is probable that the same fundamental relationship between temperature, metabolism and circulation holds for the normal tissues also.

Since heat produces an elevation of the metabolism of the tissues, its use to promote an increase in circulation must be viewed from the standpoint of the functional capacity of the vessels. If there is organic obstruction to the flow of blood, the increase in tissue needs occasioned by the elevation in temperature may be greater than any possible improvement in circulation. An additional source of injury is presented by the fact, pointed out by Starr,⁹ that the impaired blood supply will not be able to carry off the additional heat supplied from without, so that the temperature of the tissues rises to heights which are in themselves injurious.

In his discussion on the use of heat in the local treatment of peripheral vascular disease Starr⁹ made the comment "It is well known that 'baking' a foot with undiagnosed peripheral vascular disease may cause gangrene. I have seen 3 instances. The possibility of damage from more moderate overheating may well be greater than has been realized." The incidence of gangrene following application of a tourniquet in Allen's¹⁰ experiments was greatly increased even by moderate elevation of temperature.

8 Freeman, N. E., and Zeller, J. W. The Effect of Temperature on the Volume Flow of Blood Through the Sympathectomized Paw of the Dog with Observations on the Oxygen Content and Capacity, Carbon-Dioxide Content, and pH of the Arterial and Venous Blood. *Am J Physiol* **120** 475, 1937.

9 Starr, I., Jr. On the Use of Heat, Desiccation and Oxygen in the Local Treatment of Advanced Peripheral Vascular Disease, *Am J M Sc* **187** 498, 1934.

10 Allen, F. M. Experiments Concerning Ligation and Refrigeration in Relation to Local Intoxication and Infection, *Surg, Gynec & Obst* **68** 1047, 1939.

The influence of temperature on pain and cyanosis was studied by Starr⁹ in 11 patients. He found that the optimum temperature for relief of pain and improvement of color lay somewhere between 30 and 34 C (86 and 93.2 F). These observations were fully confirmed by our experience. In 8 patients with obliterative vascular disease, even though no open lesion was present at the time of observation, a temperature of 42 C (107.6 F), which was reached by gradually heating the bath in which the extremity was immersed, either brought on or increased the local pain and always increased the cyanosis. Certain patients could not tolerate even temperatures of 35 C (95 F). In 1 patient it was of particular interest to observe that the pain experienced in the finger at 40 C (104 F) persisted for two minutes after the hand had been removed to the room air. After reproducing the pain by a second heating, it was relieved in fifteen seconds by immersion of the hand in cold water.

Although pain in peripheral vascular disease is frequently aggravated by cold and relieved by warmth, there are some patients who will seek comfort by uncovering their feet. Their objection to the application of heat is significant. The discomfort of unregulated heat is complained of. Two patients have recently been observed in whom after occlusion of the femoral artery heat was applied directly to the leg by means of a baking cradle. In each instance extensive gangrene of the foot developed, and the anterior surface of the leg which was more exposed to the radiant heat showed the more intense reaction. Next to those whose gangrene is due to infection and the necrosis which results from the application of a strong antiseptic, the greatest number of patients with gangrene who are seen in the clinic for peripheral vascular diseases seem to have had their trouble precipitated by the injudicious application of heat.

What is the optimum temperature for an extremity which is the seat of occlusive vascular disease? It is well known that cold produces vasoconstriction both through reflex action of the sympathetic nervous system and directly through its action on the smooth muscle of the blood vessels. It is desirable, therefore, to avoid cold if possible, unless temporary refrigeration of the part is desired before amputation, as suggested by Allen¹⁰. On the other hand, according to the present concept, heat is harmful. Each patient probably has a specific tolerance dependent on the capacity of his vessels to supply blood to the part. Again, the metabolism of the part is conditioned by the presence of infection. The oxygen-carrying capacity of the blood is also of significance. With so many variables, it is impossible to give any definite rule as to the optimum temperature. In general, it may be said that the temperature should be maintained at the highest level which does not increase the circulatory discrepancy as shown by cyanosis and pain.

Inspection of figure 2 indicates that the curve for the increase in blood flow with rising temperature ascends sharply at temperatures higher than 30 C (86 F). From this point upward, there is a rapid increase. It is better to maintain the temperature of the air about the foot somewhere between 30 and 34 C (86 and 93.2 F). With gangrene or with gangrene impending, the temperature must be kept at a lower figure.

When wet dressings are indicated, their temperature should be carefully controlled, since heat can be more readily delivered to the tissues by hot water than by hot air. It has been our practice to apply hot wet compresses to the inflammatory area above the zone of potential gangrene but to apply moist dressings at room temperature to the distal parts.

Many devices have been suggested for the regulation of the temperature of the environment about an extremity affected with occlusive vascular disease. Starr¹¹ and Sevringhaus¹² devised excellent thermoregulated cradles. The only drawbacks are the expense of these cradles and the difficulty of accurate regulation. The simplest one which I have found is that suggested by Montgomery and Starr¹³. The thermostat is calibrated from 85 to 105 F. My associates and I have encountered no unfortunate reactions in the past two years using these thermoregulated cradles.

SUMMARY

Gangrene results from a discrepancy between the demands of the tissues and the supply of blood to meet these nutritional needs.

Experimental investigations of the effect of temperature on the volume flow of blood through sympathectomized extremities indicate that the circulation is conditioned by the metabolic requirements of the tissues.

The metabolism of the tissues increases directly with the temperature.

In the presence of organic occlusive vascular disease, the application of unregulated heat may precipitate gangrene, since it may increase the metabolism of the tissues more than it increases the circulation.

Use of a thermoregulated cradle of simple construction is suggested in order to maintain the environmental temperature at the desired level.

11 Starr, I., Jr. A Thermoregulated Foot Cradle for the Treatment of Peripheral Vascular Disease, *Proc Soc Exper Biol & Med* **29** 166, 1931.

12 Sevringhaus, E. L. A Constant Temperature Foot Cradle, *Am J M Sc* **187** 509, 1934.

13 Montgomery, H., and Starr, I. Four Physiotherapeutic Devices for the Treatment of Peripheral Vascular Disorders, *Am J M Sc* **197** 485, 1939.

EFFECT OF ESTROGENS ON VASCULAR SPASM DUE TO ACTIVE ANGIITIS IN THE EXTREMITIES

LOUIS G HERRMANN, M D

AND

EDWARD J McGRATH, M D

CINCINNATI

Recent advances in the management of arterial insufficiency in extremities have come largely as a result of better understanding of the pathologic physiology of the peripheral circulation and recognition of the more important factors which alter the delicate functional balance in the peripheral vascular bed. Disturbances in the peripheral circulatory balance greatly interfere with the natural ability of the vascular system to respond properly to the usual physical changes in the environment.

Active inflammation of the arteries or the veins in an extremity may provoke vasomotor instability in the entire limb and occasionally in all four extremities. In the early stages of peripheral angitis, abnormal susceptibility to mild degrees of cold may be the only clinical evidence of inflammatory involvement of the arteries and veins, yet if the true nature of such an underlying process is not recognized or if adequate therapy is delayed too long, serious structural changes in the affected blood vessels are certain to take place. We believe that careful studies of circulatory efficiency in the extremities, made under controlled conditions of temperature and humidity,¹ will usually enable the clinician to estimate satisfactorily how much of the circulatory embarrassment is due to reflex vasoconstriction, as well as how much actually results from structural changes in the peripheral arteries.

After a major or a secondary artery of an extremity has become obliterated by inflammatory changes in its wall or by formation of a blood clot within its lumen, the chance to restore its normal function has been lost. When circulatory insufficiency in the extremity is present as the result of such structural changes in the arteries, all thera-

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1 Herrmann, L. G. Clinic on Peripheral Vascular Diseases, Internat. Clin. 3 171 (Sept.) 1937.

peutic efforts must be directed toward promotion of a more active flow of blood through the existing collateral arteries if any permanent increase in nourishment of the tissues of the distal parts of the extremity is to be brought about

The vasomotor instability which occurs during the early phases of thromboangitis obliterans is well known. Some years ago it was considered so important in the symptomatology of this pathologic entity that "sympathetic ganglionectomy" or ramisection was suggested for its relief. At present most students of this problem believe that such operations accomplish only a little more than can be accomplished by much simpler means, therefore the practice of performing a sympathectomy for this condition has been abandoned by most surgeons.

In clinical practice one may observe a great variety of bizarre vascular disturbances, most of which cannot be classified accurately in the light of present knowledge. Rational treatment, therefore, may become extremely difficult or even impossible. Careful analysis of the obscure vascular problems presented frequently brings out the fact that the clinical picture is actually the result of several different disturbances. Since the true cause of any of the major peripheral vascular diseases has never been established, it becomes doubly important to recognize the major factors which contribute to vascular insufficiency in the extremity of any given patient and to direct the intensive treatment along known physiologic lines.

Since 1932 we have been interested in determining the various factors which cause high grade peripheral vasoconstriction and particularly in determining the various ways by which such secondary vasoconstriction can be altered for therapeutic reasons.

SECONDARY VASOMOTOR INSTABILITY

Most workers in the field of peripheral vascular disturbances have been impressed by the importance of vasomotor instability in all of the serious varieties of active vascular disease of the organic type, and many different ways of overcoming the associated peripheral vasoconstriction have been used successfully in the clinical management of these disturbances.

The vasomotor instability which usually results from the more extensive types of acute phlebitis and active arteritis has been shown also by many different observers to be responsible for many of the signs and symptoms. Frequently the secondary manifestations make up that part of the clinical syndrome toward which all active treatment must be directed if the more serious complications are to be avoided.

In 1932, Albert² published clinical and experimental proof that a high degree of peripheral arterial spasm results from acute occlusion, due to trauma or inflammation, of the major vein of an extremity. On the basis of these studies and of observations of their own, Leriche and Kunlin³ suggested infiltration of the regional sympathetic ganglions with 2 per cent solution of procaine hydrochloride to overcome the secondary vasoconstriction. Their reports indicate that most of their patients were relieved of their symptoms by this paralysis of the vaso motor nerves to the affected extremity. Recently Ochsner and DeBakey⁴ confirmed these studies and reported on several patients with thrombophlebitis who benefited greatly from blockage of the regional sympathetic pathways by procaine hydrochloride.

The apparent sex limitation of that type of active angitis called by Buerger thromboangitis obliterans has interested all students of these disturbances and has seemed to support the idea that the "hormone" content of the tissues in the male and in the female is of importance.

EXPERIMENTAL BACKGROUND

In 1935, one of us (McGrath)⁵ published the results of his work, done in 1933 and 1934, on the effect of estrogenic substances on experimental peripheral gangrene, and this work actually formed the foundation for the present clinical studies of the effect of estrogenic substances on the vasomotor instability usually observed in the early stages of thromboangitis obliterans. Using ergotamine tartrate as a toxic agent and following the experiments of Rothlin (1923) and Polak (1928), one of us (McGrath) produced lesions of the peripheral arterial and venous pathways of the tail of the albino rat. These have been described previously.⁵ Briefly, there resulted profound cellular proliferation and swelling of the intima, both arterial and venous, most pronounced in the smaller radicles on both sides of the vascular tree (fig 1). In addition, marked thrombophlebitis and periphlebitis were observed.

2 Albert, F. Les obliterations arterielles. Étude physio-pathologique, Lyon chir **29** 649 (Nov-Dec) 1932.

3 Leriche, R., and Kunlin, J. Traitement immediat des phlebitis post-operatoires par l'infiltration novocaïnique du sympathique lombaire, Presse med **42** 1481 (Sept 22) 1934.

4 Ochsner, A., and DeBakey, M. Treatment of Thrombophlebitis by Novocaine Block of Sympathetics, Surgery **5** 491 (April) 1939.

5 McGrath, E. J. Experimental Peripheral Gangrene. Effect of Estrogenic Substance and Its Relation to Thrombo-Angitis Obliterans, Arch Int Med **55** 942 (June) 1935, Experimental Peripheral Gangrene, J A M A **105** 834 (Sept 14) 1935.

With the basic lesions established, parallel series of normal control animals, unprotected animals intoxicated with ergotamine tartrate and protected by daily administrations of estrone (theelin) were studied. It is sufficient to summarize the results. All the rats, male and female, unprotected by the estrogen and intoxicated with ergotamine tartrate had gangrene of the tail in greater or less degree, varying with the

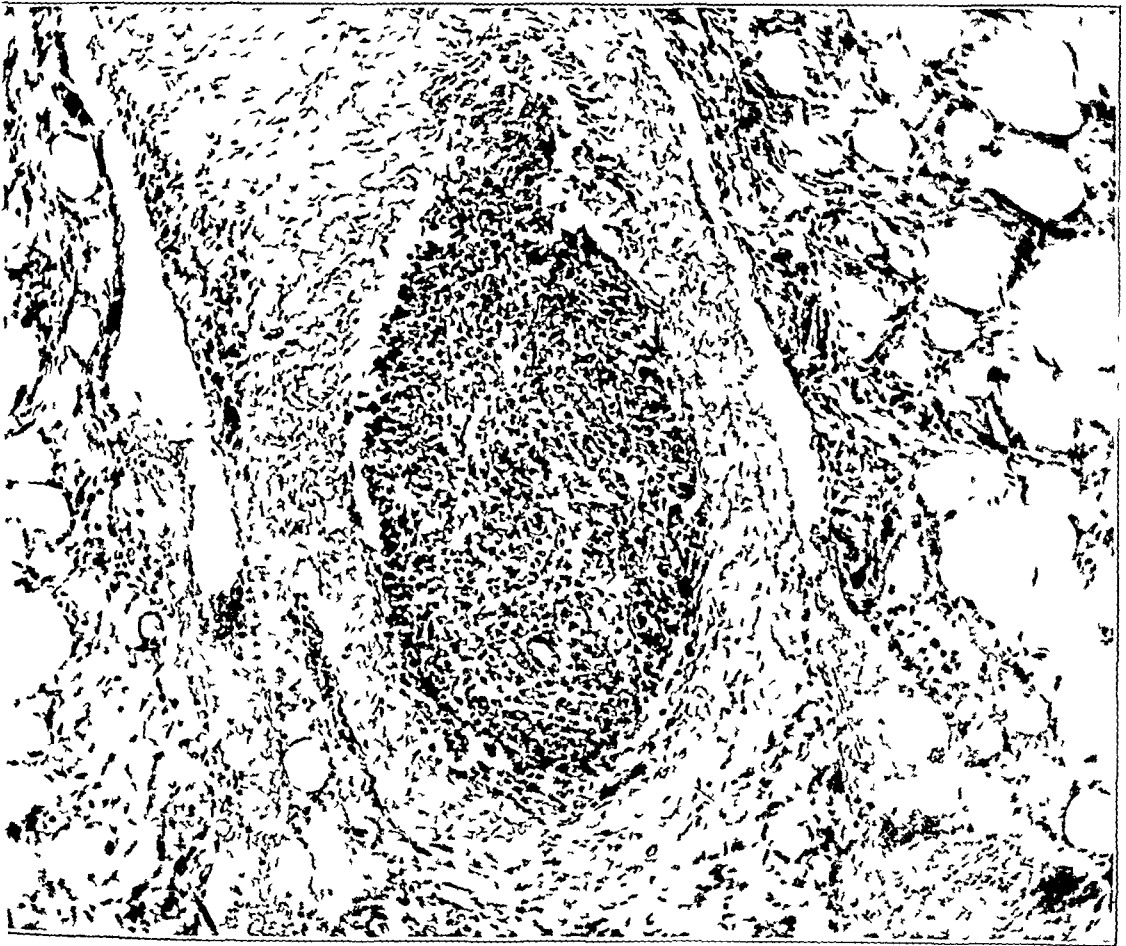


Fig 1—Cross section of the tail of an albino rat after intoxication with ergotamine tartrate. Note the thrombosis of the central artery. Magnification $\times 200$.

amount of ergotamine employed (fig 2). Conversely, female animals similarly intoxicated but protected with adequate estrogen did not have gangrene. Male animals, however, failed to respond to estrogenic therapy, becoming gangrenous in a fashion similar to unprotected males.

These results were corroborated by Suzman, Freed and Prag⁶ in 1938, and the experiment was carried through the next logical step. Investigating the effect of castration on the male, these authors found that castration alone was inefficient in protecting the animals against ergotamine gangrene. However, it was found that administration of estrone to castrate male animals produced the same protective action that we had observed previously in female rats.

CHOLINERGIC ACTION OF ESTROGENIC SUBSTANCES

Markee⁷ and Fagin and Reynolds^{7a} demonstrated that when estrogen was injected into ovariectomized rabbits maximal hyperemia developed in the uterine tissues within thirty to sixty or more minutes. The little known fact, demonstrated by Pompen,⁸ that the initial hyperemia

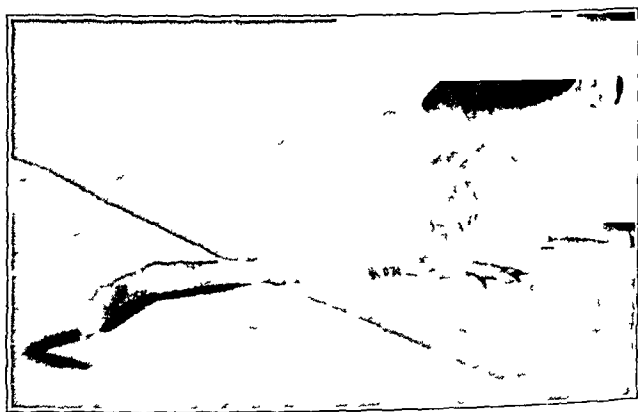


Fig. 2—Rat's tail twenty-two days after injection of ergotamine tartrate. Note the gross evidence of phlebitis proximal to the line of demarcation of the gangrene.

could be inhibited temporarily in unanesthetized rabbits by injection of atropine suggested to Reynolds⁹ that the primary agent which initiated that series of changes, particularly the vasodilatation, might be acetylcholine. His experimental studies show unmistakably that the

6 Suzman, M. M., Freed, C. C., and Prag, J. J. Studies on Experimental Peripheral Vascular Disease with Special Reference to Thrombo-Angitis Obliterans, *South African J. M. Sc.* **3** 29 (Jan.) 1938.

7 Markee, J. E. Rhythmic Vascular Uterine Changes, *Am. J. Physiol.* **100** 32 (March) 1932.

7a Fagin, J., and Reynolds, S. R. M. Local Vascular Changes and Uterine Motility, *Am. J. Physiol.* **117** 86, 1936.

8 Pompen, A. W. M. De invloed van menformon op der baarmoeder, *Thee* Amsterdam, 1933.

9 Reynolds, S. R. M. The Cholinergic Action of Oestrin, *Science* **87** 3 (June 10) 1938.

acetylcholine content of the uterus was increased significantly within one hour after the injection of estrogen (amniotin). Since the effect occurred in a transplanted uterus, connection with the central nervous system is not essential, although in his experiments sufficient time had not elapsed for complete degeneration of the nerves. In the sense, therefore, that certain nervous effects on effector organs are mediated by local liberation of acetylcholine and accordingly are said to be "cholinergic," Reynolds⁹ concluded that estrogen is similarly "cholinergic." Hence he concluded that this term must be broadened to include possible hormonal effects which are mediated peripherally by acetylcholine. In this way one could explain the maximal hyperemia which occurs experimentally in uterine transplants in which no nerves are demonstrated.⁷ The high estrogen content associated with the high acetylcholine content of human placenta¹⁰ in the complete absence of nerves could be explained also in that manner.

CLINICAL STUDIES

The results of these experimental observations encouraged us to study the clinical effects of estrogenic substances in patients with the active types of angitis, much as Baecke and Sicard did in 1927. Our primary interest, however, centered around the effect of these substances on the vasomotor instability which is secondary to primary disease of the arteries or veins of the extremities. We had observed in previous clinical studies that occasionally the propagation of intravascular thrombosis with resultant spread of the pathologic changes in the walls of the arteries or veins was enhanced by slowing of the peripheral circulation due to widespread vasoconstriction, consequently we concluded that any lessening of irritability of the peripheral vasomotor system from within the organism might lessen the chance for extension of involvement of the peripheral vessels. Our clinical studies consisted mainly of repeated examinations of the peripheral vascular system before and after complete vasomotor relaxation in the "constant temperature room" (20 C) to determine the kind and degree of changes in vasomotor control of the peripheral arteries and arterioles which developed during and after intensive treatment with estrogens.

The sustained effect of the estrogenic substances in this group of patients was found to come on slowly over a period of days, and little, if any, change in vasomotor function was ever detected in the hands or feet after administration of a single large dose or any series of smaller doses given over a period of hours. It has been shown that when estrogens are injected directly into the venous system they

¹⁰ Chang, Hsi Chun, and Gaddum, I. H. Choline Esters in Tissue Extracts
[Physiol 79:255 (Oct 6) 1933]

rapidly disappear from the circulating blood. They must be injected, therefore, in such a way that absorption will take place slowly and the effect will be prolonged over a period of days. Much remains to be done in the study of estrogenic substances in relation to the maintenance of concentration of estrogen during several weeks or months. Daily injections of water-soluble preparations by no means approximate the normal secretion of estrogen. Considerable evidence exists that an effective level of concentration of estrogen can be best maintained by injection of an estrogenic substance in oil or in some other medium less rapidly absorbed than water. The rapid retrogression of hormonal effects on cessation of injections in the experimental animals and the rapid drop in excretion of estrogens after parturition indicate that there is little or no storage of these hormones in the body.

A distinct difference in response to estrogens has been noted in the male as compared with the female. Much more estrogen is needed, or administration must be carried over a longer period, to bring about clinical improvement in males. This is also true of the experimental studies on animals. The use of testosterone propionate for some male patients has given encouraging results, but further work will have to be done before any positive information concerning its use for this type of vascular problem can be presented.

OUTLINE OF THERAPY

In the management of all forms of arterial insufficiency in extremities, general measures for protection of the skin of the affected limbs against all forms of trauma, as advocated by Allen,¹¹ Reid¹² and others, must be considered of paramount importance. The serious complications which frequently follow in the wake of arterial insufficiency due to secondary vasospasm from any form of acute angitis or phlebitis in the extremities are usually precipitated by some form of physical, chemical or thermal trauma to the affected parts.

We have employed an oily preparation of estrone (ampules theelin in oil, Parke, Davis & Co.) and have administered it intramuscularly to all patients included in this study. During the early part of our clinical work we used relatively small amounts of the estrogen (2,000 international units) at weekly intervals, but later studies showed that a more sustained effect followed prolonged administration of larger amounts. At present we are giving 4,000 international units of theelin (estrone) twice each week for four weeks and then 4,000 international units

11 Allen, A. W. The General Management of Circulatory Disorders of the Extremities, *New England J. Med.* **204** 859 (April 23) 1931.

12 Reid, M. R. The General Care of Peripheral Vascular Diseases, *Ann. Surg.* **96** 733 (Oct.) 1932.

once each week for the subsequent twelve weeks. This amount given in sixteen weeks has been designated in this work as a course of treatment.

All of our patients were taught how to care for the skin of their hands and feet and how to protect them from all forms of trauma. Abstinence from the use of tobacco in all forms was considered essential. About half the patients had stopped smoking on the advice of other physicians weeks or months prior to the beginning of treatment with estrogenic substances. The others stopped smoking at the beginning of the first course of treatment with estione (theelin) therapy. An attempt was made to remove as many of the exogenous factors as possible before the active treatment was started.

A rest of from two to six months is prescribed, during which time all the other measures of general care are carried out and the extremities are protected from the cold at all times. Patients are permitted to be moderately active but are cautioned about overfatigue. They are instructed to return for regular follow-up examination and study.

ANALYSIS OF CLINICAL RESULTS

As the basis for this report, a series of 16 patients with arterial insufficiency due to secondary vasomotor instability associated with active arteritis or phlebitis were studied and then treated by parenteral administration of moderate quantities of estrogen (estione, or theelin) at regular intervals for at least sixteen weeks.

It is extremely difficult to evaluate properly all the changes which occur as the result of any therapeutic agent or regimen, especially when one is dealing with disease processes which are known to show periods of spontaneous remission as well as of spontaneous exacerbation and which have been shown to be influenced by a variety of exogenous and environmental factors.

All the patients referred to in this report have been studied at regular intervals, and the final decision as to the condition of the patient was based on the results of objective studies of the efficiency of the peripheral vascular system and on analysis of the patient's account of the effects on the signs and symptoms of a variety of different environmental conditions.

A summary of the data concerning the 16 patients of this series is given in table 1. Two women and 1 man showed marked secondary vasospasm in the lower extremities, due to acute thrombophlebitis. No attempt has been made to differentiate between men with active migrating phlebitis and those with early thromboangitis obliterans, since marked secondary vasoconstriction was associated with both types of processes.

Pain was pronounced in 12 of the patients, and these were given moderately large amounts (50 mg intravenously each day for five days) of thiamin chloride (vitamin B₁) in addition to the estrogenic substances

We have not attempted to make any correlation between the number of international units of estrone (theelin) administered and the degree of improvement which followed the treatment. All of the

TABLE 1—Data on Patients with Secondary Vasomotor Instability in the Extremities Before Treatment with Estrogenic Substances

Statistical Information					Signs			Symptoms		
Patient	Diagnosis	Age	Sex	Parts Affected	Pallor	Cyanosis	Rubor	Pain	Numbness	Tingling
1	T A O *	29	M	Feet	++++	++	+++	++++	+++	+++
2	T A O	27	M	Feet	++++	++	++++	++++	+++	+++
3	T A O	27	M	Hands and feet	++++	+++	++	++++	+++	+++
4	T A O	41	M	Feet	++	+++	++++	++++	+++	+++
5	Phlebitis	25	F	Feet	++++	+++	0	++++	+++	++
6	T A O	24	M	Feet	++++	++	+	+++	++	+
7	T A O	41	M	Feet	++++	++	++	++	+++	+++
8	T A O	30	M	Fingers	+++	+++	0	++++	++	+++
9	T A O	34	M	Feet	++++	++	0	++++	+++	+++
10	Arteritis	52	M	Fingers	++++	++++	++	++++	++++	++
11	Phlebitis	40	F	Feet	++++	++	0	++++	++	++
12	T A O	46	M	Feet	++++	+++	++++	++++	+++	++
13	T A O	19	M	Feet	++++	++	+++	++	+++	++
14	T A O	42	M	Feet	+++	++	0	++	+++	++
15	Phlebitis	48	M	Feet	+++	++	0	++	+++	++
16	Thrombosis	30	F	Fingers	++++	++++	0	++++	++++	+++

* Thromboangitis obliterans

TABLE 2—Clinical Results of Treatment with Estrogenic Substances

	Patient No *																Percentage
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Improved	+	+	+	+	+		+		+		+	+	+		+		± ⁶⁰
Unchanged						+				+				+		+	± ²⁰
Worse								+									± ⁶

* Same patients as in table 1

patients listed as improved have been able to return to their work. Either the vasomotor instability completely disappeared, or the disease process remained so quiescent that the patient was caused no great disability or concern. Vascular studies of these patients showed a more nearly normal vascular response under natural environmental conditions as well as under the controlled conditions (normothermia) in the constant temperature room.

Of these 16 patients, 11, or 69 per cent, definitely were improved (table 2). The signs of vasomotor instability in the digits became much less marked. The pain in the digits showed corresponding

improvement, and the disability was reduced to a negligible level in most cases. In 3 patients recrudescence of the signs and symptoms occurred after two years of relief, but the activity of the process again subsided, although less completely, after another course of treatment with the estrogenic substances. In 4 patients, or 25 per cent, the symptoms have remained unchanged after many months of observation. In 1 patient, or 6 per cent, the symptoms continued to grow worse in spite of all our therapeutic effort.

SUMMARY

A total of 16 patients with marked secondary vasoconstriction associated with active angitis in the extremities has been studied and then given estrogens as the primary therapeutic agent. In this review of our experiences, an attempt has been made to present our interpretation of the benefits which have resulted after a careful analysis of the patient's account of the subjective benefits together with the objective evidence of importance we have gathered from repeated vascular studies. It must be emphasized that 3 patients of this series who had active thromboangitis obliterans have returned after several years with reactivated acute angitis.

The cholinergic effect of the estrogenic substances appears to supply only a partial explanation of these clinical results. What other effects may be exerted on the diencephalic vasomotor centers through the primary effect of the estrogenic substances on pituitary function is a problem for further study. It is a clinical fact, however, that all patients do not react alike to these substances, and the apparent difference between the reaction of the male organism and that of the female might be explained on the basis of less intense action on the central vasomotor centers. We simply wish to record, without further comment, these moderate differences in reaction between males and females and between males of different constitutional makeup.

We do not wish to draw any conclusions from the study of such a small series of patients presenting such varied clinical syndromes, nevertheless, after making these studies, we can see that the problem is worthy of more careful study and thought, and we believe that in this conclusion lies whatever value there may be in the present report.

SPEED OF BLOOD FLOW IN THE ARTERIES AND IN THE VEINS OF MAN

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Methods used since 1922 for determining the speed¹ with which blood flows in man depend for the most part on production of a reaction in one part of the body (for example, the tongue) to a substance injected into a vein in another part of the body (for example, the median basilic vein). The time elapsing between injection of the substance and detection of the reaction is known as circulation time.

Substances used are potassium ferrocyanide,² an active radium deposit,³ calcium salts,⁴ magnesium sulfate,⁵ dehydrochloric acid,⁶

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1 The term "speed" lacks accuracy, but its use is justified by convenience. If used accurately, it must embody two measurements, distance and time. In our studies no measurements of distance were made, but since those distances studied are roughly equal among different patients and since the term "speed" can be used much more conveniently than other more nearly accurate ones, it has been used advisedly in this presentation.

2 Koch, E. Die Stromgeschwindigkeit des Blutes. Ein Beitrag zur Arbeitsprüfung des Kreislaufes, *Deutsches Arch f klin Med* **140** 39-66 (July) 1922.

3 Blumgart, H. L. The Velocity of Blood Flow in Health and Disease. The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, *Medicine* **10** 1-75 (Feb) 1931.

4 Hirschsohn, J., and Maendl, H. Notiz zur Kenntnis der Hämodynamik beim Pneumothorax, *Beitr z Klin d Tuberk* **49** 64-75, 1921. Kahler, H. Ueber Veränderungen der Blutumlaufzeit (Ein Beitrag zum Problem der Blutgeschwindigkeit), *Wien Arch f inn Med* **19** 1-38 (Oct 25) 1929. Goldberg, S. J. The Use of Calcium Gluconate as a Circulation Time Test, *Am J M Sc* **192** 36-41 (July) 1938.

5 Neurath, O. Untersuchungen über die Bestimmung der Blutumlaufgeschwindigkeit mit Magnesiumsulfat, *Ztschr f klin Med* **132** 134-143, 1937. Bernstein, M., and Simkins, S. The Use of Magnesium Sulfate in the Measurement of Circulation Time, *Am Heart J* **17** 218-237 (Feb) 1939.

6 Winternitz, M., Deutsch, J., and Brull, Z. Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion (Kurze Mitteilung), *Med Klin* **27** 986-988 (July 3) 1931. Gargill, S. L. The Use of Sodium

saccharin,⁷ various dyes,⁸ ether,⁹ histamine¹⁰ and sodium cyanide¹¹ These substances have been used chiefly for determining the speed of blood flow in a pathway consisting of peripheral veins, pulmonary arteries and veins, chambers of the heart and part of the arteries originating from the left ventricle The circulatory pathway from the arm to the tongue is a good example Because a solution¹² containing magnesium sulfate, calcium gluconate and sodium chloride produces a sensation of warmth in the extremities when it is injected

Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, *New England J Med* **209** 1089-1093 (Nov 30) 1933 Tarr, L, Oppenheimer, B S, and Sager, R V The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am Heart J* **8** 766-786 (Aug) 1933

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8 Hamilton, W F, Moore, J W, Kinsman, J M, and Spurling, R G Simultaneous Determination of the Pulmonary and Systemic Circulation Times in Man and of a Figure Related to the Cardiac Output, *Am J Physiol* **84** 338-344 (March) 1928 Klein, O, and Heinemann, J Zur Messung der Stromungsgeschwindigkeit des Blutes beim Menschen, *Zentralbl f inn Med* **50** 490-493 (May 25) 1929 Thompson, W O, Alper, J M, and Thompson, P K The Effect of Posture upon the Velocity of Blood Flow in Man, *J Clin Investigation* **5** 605-609 (June) 1928

9 Hitzig, W M Measurement of Circulation Time from Antecubital Veins to Pulmonary Capillaries, *Proc Soc Exper Biol & Med* **31** 935-938 (May) 1934, The Use of Ether in Measuring the Circulation Time from the Antecubital Veins to the Pulmonary Capillaries, *Am Heart J* **10** 1080-1095 (Dec) 1935

10 Weiss, S, Robb, G P, and Blumgart, H L The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, *Am Heart J* **4** 664-691 (Aug) 1929

11 (a) Robb, G P, and Weiss, S A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *Am Heart J* **8** 650-670 (June) 1933 (b) Smith, L A, and Allen, E V Unpublished data

12 (a) Kvale, W F, and Allen, E V The Rate of the Circulation in the Arteries and Veins of Man I Studies of Normal Subjects and of Those with Occlusive Arterial Disease and Hyperthyroidism, *Am Heart J* **18** 519-536 (Nov) 1939 Kvale, W F, Allen, E V, and Adson, A W The Rate of Circulation in the Arteries and Veins of Man II Studies of Hypertension, of Orthostatic Hypotension, and of the Effects of Sympathectomy, *ibid* **18** 537-545 (Nov) 1939 Kvale, W F, and Allen, E V The Rate of the Circulation in the Arteries and Veins of Man III The Influence of Temperature of the Skin, Digestion, Posture and Exercise, *ibid* **18** 546-556 (Nov) 1939, IV An Error in the Sodium Cyanide Method of Determining Speed of Venous Blood Flow, *ibid* **18** 557-561 (Nov) 1939 (b) Spicer, L C, Wright I S, and Saylor, L A New Method for Determining the Circulation Time Throughout the Vascular System A Preliminary Report, *ibid* **12** 511-520 (Nov) 1936

intravenously, we have used such a solution in an attempt to estimate the speed of the flow of blood in peripheral arteries. Because a solution of sodium cyanide¹¹ when injected intravenously produces a sudden gasp by action on the carotid sinus, we have used such a solution to estimate the speed of blood flow in peripheral veins. It is our purpose in this paper to report the results of these studies.

TECHNIC

Use of a solution containing magnesium sulfate, calcium gluconate, sodium chloride and copper sulfate, which was introduced by Spier, Wright and Saylor,¹² has been discussed by them and by two of us (Kvale and Allen^{12a}). When this solution is injected intravenously, it produces a sensation of warmth in the tongue (or throat), perineum, hands and feet of the subject. The subject is informed of the type of reaction he is to experience and is instructed to report immediately the site of the sensation by saying "tongue," "crotch," "hands" or "feet," according to the region in which the first sensation arises.¹³ When the sensation occurs in the hands, it usually occurs in the two simultaneously. The same usually is true of the feet. However, the sensation may occur in one hand before it does in the other and in one foot before the other, and in such cases the subject designates the site by saying "right hand" or "left hand" and "right foot" or "left foot."

The subject is supine in bed, with the arm at the level of the heart. A tourniquet is applied. Two cubic centimeters of the solution is drawn into a 3 cc syringe which has been fitted with a 20 gage needle. The needle is then inserted into a vein overlying the antecubital fossa, the tourniquet is removed and after three to five seconds the solution is injected as rapidly as possible. When the injection is started, the person performing the test says "Go," and an assistant starts the stopwatch. The circulation time is recorded as the subject calls out the various places at which the sensation is perceived. The time elapsing between the beginning of injection of the solution into a vein at the elbow and the occurrence of the sensation of warmth in the throat, perineum, hands and feet is determined. We do not know that occurrence of the sensation of warmth in the hand, for instance, indicates that the solution has concurrently arrived at the hands, but for the purpose of simplification we have assumed that this reasoning is correct. The expressions "arm to hand" and "arm to foot" indicate the time elapsing between the beginning of the injection into a vein at the elbow and the sensation of warmth in the hands and in the feet respectively. Occasionally subjects have been unable to perceive the sensation, in such cases the term "blank" has been used. Such a study as the present one does not allow determination of the velocity of the flow of blood in the arteries, for there is no way of knowing when the solution leaves the left ventricle. However, this can be estimated with reasonable accuracy. By the time the solution reaches the tongue from the left ventricle, it probably has traversed the aorta for a distance equal to that traversed to the tongue. The time required for the blood to traverse this distance appears to be about one second, although this has not been accurately established. Because this time is relatively constant and relatively short, we have eliminated it from our calculations and have assumed that when the sen a

13 It seems worth while to emphasize that in this paper a decrease in circulation time indicates an increased velocity of blood and that an increase in circulation time indicates a decreased velocity of blood.

tion of warmth occurs in the tongue the solution is leaving the left ventricle. We therefore estimate the circulation time from the left ventricle to the perineum by subtracting the "arm to tongue time" from the "arm to perineum time." The "ventricle to hand time"¹⁴ is calculated by subtracting the "arm to tongue time" from the "arm to hand time", the "ventricle to foot time," by subtracting the "arm to tongue time" from the "arm to foot time." The figures thus obtained are subject to the qualification which we have noted. They afford us, for the first time, approximately correct figures for determining the speed of blood flow in peripheral arteries.

In studying the venous circulation time it was desirable to use a method which was simple, easily performed and objective. Injection of measured quantities of 2 per cent sodium cyanide solution was made in the antecubital veins and in the veins of the foot or ankle. The time as measured by a stopwatch between the beginning of the injection and the occurrence of a sharp respiratory stimulation constituted the circulation time from the point of injection by the shortest pathway to the carotid sinus.

NORMAL CONDITIONS

With normal subjects, the average for 87 determinations of the "arm to carotid sinus time" (with sodium cyanide) was twenty and eight-tenths seconds. The average for 102 determinations of the "arm to tongue time," (with the solution of calcium, magnesium and sodium salts) was thirteen and seven-tenths seconds. When the two solutions were mixed it was found that sensation was perceived in the tongue at an average of three and one-half seconds before a gasp resulted from stimulation of the carotid sinus by the sodium cyanide. We have concluded that there is an error inherent in the sodium cyanide method and that values obtained by such a method are approximately three and one-half seconds greater than they should be. The average figures for other circuits follow: arm to perineum, twenty-one seconds, arm to hand, twenty-three and one-half seconds, arm to foot, thirty-two seconds, ventricle to perineum, seven and three-tenths seconds, ventricle to hand, nine and eight-tenths seconds, ventricle to foot, eighteen and a half seconds, and foot to carotid sinus, thirty-nine seconds.

CHRONIC OCCLUSIVE ARTERIAL DISEASE

A study of 28 cases of thromboangitis obliterans and arteriosclerosis obliterans indicates that when a subject has these diseases the average time required for blood to flow to the feet is increased (the approximate mean "ventricle to foot time" for subjects with these conditions was twenty-four seconds, as contrasted with a normal value of eighteen and one-half seconds). However, in individual instances of chronic occlusive arterial disease the circulation time seemed normal. Therefore, tests of the speed of arterial circulation cannot be employed in arriving at diagnoses of chronic occlusive arterial diseases.

¹⁴ Throughout the paper the term "ventricle," used as it is used here, refers to the left ventricle.

HYPERTHYROIDISM

The speed of blood flow is increased in the presence of hyperthyroidism. In thirty-one tests of 14 patients with the condition the average circulation time from the arm to the tongue was ten and four tenths seconds, from the ventricle to the perineum, four and six-tenths seconds, from the ventricle to the hand, about six seconds, and from the ventricle to the foot, about eleven seconds. These periods are shorter by approximately three, three, four and seven seconds respectively than those observed in similar tests of normal subjects. Administration of 4 to 6 grains (0.26 to 0.4 Gm.) of desiccated thyroid substance daily for four days changed the average "foot to carotid sinus time" from forty to twenty-nine seconds and the average "arm to carotid sinus time" from twenty to sixteen seconds.

ESSENTIAL HYPERTENSION

The speed of blood flow in patients with uncomplicated essential hypertension agrees with that in normal subjects. The average values determined by a study of 37 subjects, follow: arm to tongue, fourteen and four-tenths seconds, arm to perineum, twenty-two seconds, arm to hand, twenty-three seconds, arm to foot, thirty-six and one half seconds, ventricle to perineum, seven and one-half seconds, ventricle to hand nine seconds, and ventricle to foot twenty-one and one-half seconds. These all may be considered normal except the circulation time from the arm to the foot and that from the ventricle to the foot, which are about four and one-half and three seconds greater respectively than similar averages for normal subjects, an observation which suggests slowing of the flow of blood to the lower extremities in the presence of essential hypertension.

EFFECT OF SYMPATHECTOMY

If sympathectomy affecting one extremity has been performed as a part of the first stage operation for relief of essential hypertension the average circulation time from the ventricle to the sympathectomized foot is nine seconds less than for the opposite, unsympathectomized extremity (twenty-five and one-half seconds). The average "foot to carotid sinus time" is thirteen and seven-tenths seconds less for the sympathectomized limb than for the normal, unsympathectomized companion member (forty-four and seven-tenths seconds). Results of these studies indicate that lumbar sympathectomy performed as a part of the operative treatment for essential hypertension increases the speed of blood flow in both arteries and veins and that vasodilatation results from sympathectomy. Two other observations are of interest. After both limbs had been sympathectomized, the circulation time for the

limb that had been sympathectomized first was increased as compared with that observed after the original operation. After both operations had been performed, the venous circulation time was less for the more recently sympathectomized limb than for that originally sympathectomized. These observations suggest that there is a gradual recovery of vascular tone in limbs to which the sympathetic fibers have been cut.

EFFECT OF TEMPERATURE OF THE SKIN OF THE EXTREMITIES

The temperature of the skin was determined with an electric thermometer. Changes in temperature of the skin were produced by various methods, such as moving the patient from a room the temperature of which was constant at 18 C into a room the temperature of which was constant at 25 C, by placing a "baker" over one extremity and producing vasodilatation and by placing a "baker" over the entire body, producing generalized vasodilatation. The rate of circulation in the peripheral arteries was always increased when the temperature of the skin was increased and decreased when the temperature of the skin was decreased. For example, in 1 instance the "arm to foot time" was forty-nine seconds when the temperature of the skin of a toe was 29.5 C and thirty-seven seconds when the temperature of the skin of a toe was 38 C. This observation emphasizes the need for controlled conditions, constant room temperature and a fasting state in determining the speed of circulation. Not infrequently when tests were performed with the solution of calcium and magnesium salts it was noticed that "blanks" occurred, that is, that the subject failed to perceive the sensation of warmth in the extremities. Some of these "blanks" were the result of confusion on the part of the subject, but many were the result of the fact that the cutaneous temperature of the extremity was relatively low. When the cutaneous temperature was increased, the subject perceived the sensation distinctly.

Our studies show that when the skin is cool the circulation time from the foot to the carotid sinus is increased, and that when the skin is warm it is decreased. For example, in 1 case, when the temperature of the skin of a toe was 20.7 C, the "foot to carotid sinus time" was forty-nine and four-tenths seconds, and when the temperature of the skin of a toe was 32.6 C, it was twenty-five and four-tenths seconds. These observations indicate that the temperature of the skin is most important in determining the speed of the flow of blood in veins.

EFFECT OF POSTURE

It was desirable to know the effect of elevation of the extremities on the circulation time from the arm to the carotid sinus and on that from the foot to the carotid sinus. Values for the former with the

vein at the level of the right auricle were compared with values obtained when the arm was supported at an angle of 30 degrees with the horizontal. The same procedure was used in testing the effect of elevation on the circulation time from the foot to the carotid sinus. Decrease of "arm to carotid time" by 12 to 20 per cent and of "foot to carotid time" by 8 to 25 per cent are the results of elevation of the extremity results which mean that venous blood flows more rapidly in an elevated extremity than in one which is horizontal. The circulation time from the ventricle to the foot was increased in almost all instances when the subject stood. In other words, arterial blood appears to flow more slowly in the legs when a subject is upright than when the subject is recumbent, a result which may be caused by orthostatic vasoconstriction in the lower extremities.

EFFECT OF DIGESTION

Studies were performed on subjects who had fasted and were repeated about two hours after the subjects had ingested a large meal. When the temperature of the skin of the digits increased as a result of digestion, the blood nearly always flowed faster. For example, in 1 instance, when the temperature of the skin of the toes increased from 27.3 to 32.8 C as a result of digestion the "arm to perineum time" decreased from twenty-six to nineteen seconds, the "arm to hand time," from thirty-two to twenty-five seconds, and the "arm to foot time," from forty-six to thirty-five seconds.

EFFECT OF EXERCISE

A standard set of exercises was used, with the subject supine to reduce the effects of other factors. Control values for the circulation time from the foot to the carotid sinus and from the arm to the carotid sinus were obtained and were redetermined within two minutes after cessation of the movements. Speeding of the flow of blood uniformly occurred in the legs after exercise. The reduction in "foot to carotid sinus time" ranged from 24 to 40 per cent. The circulation time remained the same after exercise of the arms in 1 subject and was even slowed in 3.

The test for circulation time from the arm to the foot was performed first when the subjects were at rest and next after the subject had ascended and descended a set of steps for one minute, after which the pulse rate was accelerated to as low a figure as 104 and to as high a figure as 140. In almost all instances the speed of blood flow in the peripheral arteries was found to be increased after exercise. For example, in 1 instance the "arm to tongue time" decreased three seconds, the "arm to hand time" three seconds and the "arm to foot time" ten seconds.

These observations show that exercise increases the speed of flow of blood in both arteries and veins.

EFFECT OF OPERATION

The effect of operation on venous circulation time was studied in a group of 31 patients, 21 men and 10 women. With all of these patients circulation time was obtained under standard conditions before operation. With 9 patients studies were made at intervals varying from two hours to ten days after the operation. The remaining 22 patients were tested at intervals varying from two to thirteen days after the operation.

Twenty-four hours after the operation, the circulation time from the arm to the carotid sinus was decreased in all instances. After the second postoperative day there was some increase of circulation time for 48 per cent of the patients, a decrease for 32 per cent and essentially no change for 20 per cent. The only distinct change in the circulation time from the arm to the carotid sinus after operation was a definite decrease during the first forty-eight hours.

Two days after the operation the average circulation time from the foot to the carotid sinus increased from its first postoperative decrease. Beginning on the fifth postoperative day, it became progressively greater until the eighth to the thirteenth postoperative day. Study of the individual patients revealed that for 82 per cent there was distinct increase, for 11 per cent a decrease and for 7 per cent essentially no change.

These observations, which will be reported in detail in the future,^{11b} indicate that the speed of blood flow in the veins of the legs is usually reduced by operation. The possible relation of this observation to post-operative thrombosis and embolism will be discussed in a subsequent publication.

SUMMARY AND CONCLUSIONS

The methods of study which we have used indicate that the speed of the flow of blood in the arteries and in the veins of the extremities is influenced by a number of factors. Chronic occlusive arterial diseases usually slow the arterial circulation but do not always do so. Hyperthyroidism increases the speed of blood flow, hypertension slows it in the lower extremities, sympathectomy speeds it greatly, as does increasing the temperature of the skin of the digits. Elevation of an extremity increases the speed of flow of venous blood, but when the subject stands the speed of flow of arterial blood is decreased. Digestion is associated with an increase in speed of blood flow, and exercise accelerates flow in arteries and veins. Operation usually reduces the speed of the flow of blood in the veins of the lower extremities.

DIABETIC GANGRENE

REVIEW OF NINE HUNDRED AND SEVENTY-TWO CASES OF GANGRENE
ASSOCIATED WITH DIABETES MELLITUS TREATED AT THE
NEW ENGLAND DEACONESS HOSPITAL

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In this paper I shall try to give a general picture of the diabetic patient with gangrene, to describe the organization for and the principles of management of cases of diabetic gangrene at the New England Deaconess Hospital and possibly, through a study of my results, to indicate how I have arrived at my present conception of the operative treatment of this condition. I do not wish to add to the many reports on the details of management of diabetic gangrene or to enter into any controversy as to the indications for amputation or the level at which it should be done.

ORGANIZATION FOR THE CARE OF "SURGICAL DIABETIC" PATIENTS AT THE NEW ENGLAND DEACONESS HOSPITAL

I did my first amputation for gangrene—a closed amputation through the upper third of the lower part of the leg—in May 1923. Insulin had been given to the first patient in the New England Deaconess Hospital the preceding August and had already completely changed the outlook for the diabetic patient in need of surgical treatment. Coma, no longer a fatal complication, had been replaced by gangrene as one of the most frequent causes of death.¹

My interest in the surgical complications occurring in patients with diabetes was encouraged by the late Dr D F Jones, to whose early concepts of the management of such conditions subsequent years and increasing experience have added little. Through the interest and generosity of Dr Elliott P Joslin, every opportunity was given to develop facilities for the study and care of patients with diabetic gangrene at the New England Deaconess Hospital. When the many time-consuming details necessary for the proper care of the patient and the importance of teaching hygiene of the foot were recognized, a graduate nurse was

¹ Morrison, in his study of 775 deaths in Boston, had previously shown that in 23 per cent of these gangrene was a contributory cause (Morrison, H Boston M & S J 175 54, 1916)

obtained and was given special training in the technic of surgical dressings and in prophylactic care of the foot. The "beauty parlor for diabetic feet" was thus established. Here the patient was not only told but taught to "keep his feet as clean as his face." It was soon found that more and more responsibility could be given the nurse in the actual dressing of the smaller "surgical" wounds. Thus the surgeon was relieved of many of the details of minor but important and time-consuming dressings. This confidence was more than justified, and as the number of patients increased it became necessary to give the nurse an assistant. The present organization, therefore, consists not only of the surgical and medical components of the team but, in addition, of two especially trained graduate nurses whose entire time is devoted to the actual care of surgical dressings under the direct supervision of my associate Dr. T. C. Pratt and me.

Early in 1924, regular weekly ward rounds were instituted at the suggestion of Dr. Joslin. Promptly at 8 a. m. each Monday, Dr. Joslin, his assistant, Dr. Howard F. Root, Dr. D. F. Jones, the nursing personnel directly responsible for the medical and surgical care of the diabetic patients and I met in the ward. Each surgical patient was seen, all the dressings were removed, and the wounds were examined. The medical and surgical problems of each patient were discussed. Questions relating to individual patients were brought up and decisions made. New advances, either medical or surgical, were presented to the group for deliberation. Throughout the period of approximately fourteen years it is doubtful that this visit has been omitted more than once a year. Its permanence is evidence of its importance and value as a common ground for surgical and medical intercourse in the management of this difficult condition.

To assure accurate data, a special surgical card is used, on which are placed the pertinent facts in relation to each case as the patient is admitted to the hospital. Postoperative notes are added at the time of discharge, and additional space is left for follow-up notes. It is from these cards that this and other, similar studies have been made.

RESUMÉ OF CASES FOR STUDY

Between May 1923 and Jan. 1, 1939, 972 patients have been seen and treated for obliterative arterial disease and diabetes mellitus.

During the same period, 319 patients have been operated on for infection of a lower extremity, but careful evaluation of the arterial supply of these patients has convinced my associates and me that, although not normal it was adequate. Their cases therefore, as suggested by Collier and Marsh,² should not be included in a discussion of cases of diabetic gangrene.

Sex—In this series, the incidence of gangrene was about equally divided between men and women. Fifty-three per cent of our patients were women, slightly less than the ratio of women (57 per cent) in Joslin's³ series.

Age—The average age of all our patients was 64.3 years, that of the women (65.2 years) being a little greater than that of the men (63.8 years).

Duration of Diabetes—The patients had had diabetes for an average of eight and seven-tenths years. The difference between the average duration for the women (nine and three-tenths years) and that for the men (eight and six-tenths years) is not significant.

It seems fair to say, then, that the average patient with diabetic gangrene may be either a man or a woman, is about 64 years old and has had diabetes for an average of about eight and a half years.

TABLE 1—*Nine Hundred and Seventy-Two Cases of Incipient or Actual Gangrene in Patients with Diabetes Mellitus (New England Deaconess Hospital, 1923-1939)*

Treatment	Number	Deaths	Mortality per Cent
No operation*	414	19	4.6
Minor amputation	63	4	6.3
Major amputation	495	69	13.9
Total	972	92	9.5

* Patients treated without operation prior to 1930 not included.

ADMISSION ROUTINE FOR SURGICAL PATIENTS

At the New England Deaconess Hospital there is no distinction between the medical and the surgical wards. Promptly after examination of the patient on admission the surgical consultant is called, and the patient is seen by Dr. Pratt or by me within a few hours. Surgical treatment is instituted at once, antidiabetic treatment already will have been started. If operation is indicated, the time at which it will be done is based primarily on the urgency of the local condition. In our earlier experience many of these conditions were treated as emergencies, and amputation was done on the day of admission. Although we still consider them emergencies in that they should be seen by the surgical consultant promptly after admission of the patient, increasing experience

2 Collier, F. A., and Marsh, P. L. Lesions of Extremities Associated with Diabetes Mellitus, J. A. M. A. 85:168 (July 18) 1925.

3 Joslin, E. P. Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger 1928, p. 139.

has shown us that it is only the occasional case in which immediate operation is needed and that sufficient delay to permit adequate fluid intake and adjustment of the metabolic imbalance is desirable. Moreover, in some cases of gangrene with active infection a waiting period of twenty-four to seventy-two hours is frequently of great help in determining the type of operation indicated. This is in keeping with the conclusions of Maes,⁴ who found that the safest time for operation is after two or three days of preparation. Since the introduction of chemotherapy, there are a few cases in which forty-eight or seventy-two hours of adequate sulfanilamide intake may make the difference between a guillotine amputation and a primary closed amputation. However, most of the patients whom we see with actual gangrene due to obliterative arterial disease have a lesion badly contaminated with a variety of organisms, the beta hemolytic streptococcus in our cases playing a relatively minor role. We cannot but feel that Meleney⁵ placed rather more stress on the bacteriologic factor in diabetic gangrene than our experience would justify.

TECHNICAL CONSIDERATIONS AND RESULTS

Approximately half the patients who come under treatment are treated without operation. Eleven and three-tenths per cent of the others have a successful amputation of one or more toes, and 88.7 per cent have a major amputation. Thirty-three patients have refused amputation and have gone elsewhere for treatment. These will be discussed later in this paper.

Level of Amputation—The indications for operation and the factors from which the level of amputation is decided were first outlined in 1928⁶ and have been reviewed more recently.⁷ In 1923, amputation through the lower part of the leg was most frequently done. During the past sixteen years, waves of enthusiasm have increased temporarily the number of amputations below the knee or the number of Gritti-Stokes amputations, but throughout this period there has been a gradual but steady trend in favor of the supracondylar amputation. As one looks at table 2 and notes the small number of amputations through the lower part of the leg in proportion to the number of those above the knee, one cannot but wonder at the sequence

4 Maes L. Personal communication to the author.

5 Meleney F L. *Surgery* 6:845, 1939.

6 McKittrick L S, and Root H F. *Diabetic Surgery*, Philadelphia, Lea & Febiger, 1928.

7 McKittrick L S. *Am J Surg* 44:46, 1939.

of events which has resulted in gradual elimination of other levels of amputation in favor of the supracondylar operation. It is possible that with the latter there are a few patients who have been unjustly denied the tremendous advantage of a knee joint. A careful study of our results, however, not only in the immediate management of the patients but after they have left the hospital, has convinced us that except in selected cases the operation which is the safest and is followed by the

TABLE 2—Results After Operation for Gangrene

Operation	No	Deaths	Mor- tality, per Cent	Healing by First Inten- tion	Wound Healing			Postoper- ative Stay in Ho- pital, Days
					Major	Sepsis		
						Minor	Unstated	
Amputation of toe	63	4	6.3	2	(Granulation, 61)			46
' Lower leg ' amputation	42	2	4.8	7	4	13	18	41
Guillotine amputation*	37	13	35.1					
Gritti Stokes amputation	104	15	14.4	23	12	15	49	31
Supracondylar amputation	330	33	11.5	165	18	33	114	90
Death under anesthesia	1	1	100.0					

* Nineteen guillotine amputations followed by amputation at a higher level are classified also under the secondary level at which amputation was done.

TABLE 3—Comparison of Results with Silk and Catgut in One Hundred and Twelve Consecutive Primary Thigh Amputations

	Number	Healing by First Intention	Sepsis			Postoperative Stay in Hospital, Days
			Major	Minor	Not Stated	
Catgut						
1939	31	30	0	0	1	1.4
1938	23	20	0	1	2	21.3
1936	2	1	0	1	0	18.0
Total	56	51 (96.2%)	0	2 (3.8%)	3	19.4
Silk						
1936	27	16	0	3	8	20.0
1937	29	23	0	1	5	27.1
Total	56	39 (90.7%)	0	4 (9.3%)	13	23.5

shortest and easiest convalescence is the procedure of choice. This, according to our experience, is the supracondylar amputation (tables 2 and 3).

Drainage of Stump—Dr. Jones was an early advocate of the circular amputation for a patient with obliterative arterial disease. He insisted particularly that if the amputation is carefully done and the fascia sutured over the end of the bone without undue tension, the insertion of a drain is of no value and in most instances is a definite hazard. As a house officer at the Massachusetts General Hospital before this teaching

had been accepted by the other members of the staff, I followed a number of amputations in which drainage had been used. Later, as assistant to Dr. Jones, I helped him with similar cases in which the wounds were carefully and completely closed. I was easily convinced then, and subsequent experience has confirmed the soundness of his judgment. In every case in this series, either a guillotine amputation has been done without any sutures or the wound has been closed without drainage.

Treatment of the Nerves—Until 1930, absolute alcohol as advocated by Huber and Lewis⁸ was injected into the nerve trunk. It was difficult to prevent some leakage of alcohol from the cut nerve. This made little, if any, difference in the center of a large thigh stump, but the common peroneal nerve is very close to the incision in a Gritti-Stokes amputation, and a little leakage may easily result in an area of necrosis of the stump. The use of alcohol was therefore discontinued, the nerve was crushed and tied (Little⁹) to avoid hemorrhage from the accompanying vessels, and the end was cauterized as advocated by Hedri¹⁰. In our opinion, either is satisfactory, we have had but one readmission to the hospital for a painful stump, and in this instance the pain was not sufficiently severe to warrant any active treatment. It is our impression that the particular group of patients under discussion will do perfectly well without any special treatment of the nerves, provided early healing without infection occurs.

Sutures—With the more recent controversy concerning the relative merits of silk and catgut, it seemed to us only a matter of time before silk sutures would be advocated as the answer to problems of wound healing in amputations for gangrene. Beginning in 1936, therefore, and continuing through 1937, fine silk was used in all amputations. We have selected cases of primary thigh amputation for comparison because we know of no other group of cases in which other factors are as constant as in this. These operations have all been done by Dr. Pratt or myself. I doubt that our technic has improved much, if any, during the past few years. We have not altered our conception of the indications for operation, the level at which amputation is done or the technic which has been used. In other words, as nearly as is clinically possible all factors except suture material are constant.

Table 3 shows comparative studies of results obtained from the use of silk and from the use of catgut. No 1 chromic catgut was

8 Huber, G. C., and Lewis, D. Amputation Neuromas. Their Development and Prevention, Arch Surg 1 85 (July) 1920.

9 Little, E. M. Artificial Limbs and Amputation Stumps, Philadelphia, P. Blakiston's Son & Co., 1922, p. 36.

10 Hedri, O. Arch f klin Chr 253 118, 1921.

placed around the popliteal artery in both series, because a large suture is necessary to crush the calcified walls of the artery. No 00 plain catgut was used for the smaller vessels, and the fascia was approximated with no 00 chromic catgut. Nonboilable sutures were used. In the "silk series," nos 3 and 5 untreated black twisted silk were used for the smaller vessels and for fascia.

In order to be classified as healing by first intention, the wound must be solidly healed and the sutures removed within twelve days. There must have been no separation of the edges of the skin, no necrosis and no suppuration around any of the sutures, the stump must not have been red, and there must have been no serum. A stump is credited with healing by first intention only when a note has been made on the surgical card to that effect. However, cases listed in the table in which a definite note was not made probably were cases in which healing occurred by first intention, since in most if not all of them the stump was recorded as healed at the time of discharge.

We realize that this group of cases is small. On the other hand, it is our clinical impression, and from a study of this small group of cases I believe we are justified in assuming, that in a supracondylar amputation for gangrene neither suture material holds any merit over the other so far as wound healing is concerned, provided that the suture used is only large enough to permit careful approximation of the fascia. Needless to say, it is gratifying to us to find that the wounds in 96 per cent of our cases of primary thigh amputation for gangrene heal so promptly and that there has been no deep infection in the stump after such an amputation during the past four years.

Duration of Stay in the Hospital—It has been our constant endeavor to select as accurately as possible the patients for whom major amputation is necessary, to do the operation as soon as the decision can be made, and to discharge the patient as early as is consistent with his welfare (table 4). The importance of the economic problem presented by diabetic persons with gangrene cannot be minimized. Two months of hospitalization is not too much to spend for a useful foot, but the unsuccessful attempt should, if possible, be recognized early and amputation at a higher level promptly carried out.

Patients who after major amputation are not going to use an artificial limb are discharged twelve to fourteen days after the operation. Patients who offer some possibility of using an artificial limb are fitted with a temporary appliance toward the end of the second week of their stay in the hospital and during the third week are taught the fundamental principles of using a peg leg.

Comparison of the length of stay in the hospital after thigh amputations (tables 2 and 3) shows how this period has been gradually shortened

Bilateral Amputations—We have done 70 bilateral amputations. This represents 16 per cent of our cases. The true incidence of bilateral gangrene will be shown later to be about 40 per cent. The average interval between discharge from the hospital and the onset of gangrene of the other leg was twenty-five and three-tenths months, which is comparable to the twenty-seven and six-tenths months to be mentioned (table 7). It is interesting to find that the result following operation

TABLE 4—*Duration of Stay in Hospital*

Type of Treatment	Preoperative Period Days	Postoperative Period, Days	Total Days
No operation			23
Minor amputation	17	46	63
Primary major amputation	8	26	34
Multiple operations for the same lesion	16	49	65

TABLE 5—*Causes of Death After Amputation for Gangrene*

Cause	Number	Per Cent
Infection	29	39.7
Cardiorenal disease	29	39.7
Pulmonary disease	13	17.8
Bronchopneumonia	6	
Embolism	7	
Miscellaneous	2	2.7
Total	77	

on the remaining extremity is definitely better than that following the first operation. Not only is life expectancy increased, but the risk of operation is less. Six, or 8.6 per cent, of the 70 patients died in the hospital after amputation of the remaining limb, as compared with the mortality of 13.9 per cent for all major amputations. It is of interest too that the total period of hospitalization for a patient admitted to the hospital with gangrene of the remaining leg is definitely less than for his first admission. The average totals are forty-eight and six-tenths days for the first admission and thirty-three days for the second. The greater safety of the second amputation, the greater life expectancy and the optimistic letters written by many of the patients who have had bilateral amputations, particularly if they have a happy home life, make one feel that the tragedy of diabetic gangrene is not amputation of the

second leg but loss of the first one. It is probable that the reasoning which prompts most surgeons to postpone amputation of the remaining extremity as long as the patient's endurance will permit is based on false premises. May it not be that the second amputation should be advised after a shorter rather than a longer trial of conservative treatment?

Deaths in the Hospital—Nine and five-tenths per cent of all patients treated for gangrene in its incipient or advanced stages have died in the hospital. Four and six-tenths per cent of the patients treated

TABLE 6—*End Results After Amputation for Gangrene in One Hundred Conservative Cases (New England Deaconess Hospital, 1923-1930)*

Present Condition	Number of Patients	Duration of Life, Months	
		Average	Mean
<i>Dead</i>			
No gangrene of other foot	55 }		
Gangrene of other foot but no operation	19 }	37.5	
Gangrene of other foot followed by 2d amputation	18	73.3	69.5
Total	92	44.5	37.5
<i>Living</i>			
Bilateral amputation	4		
Trouble with other foot	1		
No trouble with other foot	2		
Total	7	133.6	133
<i>Untraced</i>	1		
	100		

TABLE 7—*End Results After Amputation for Gangrene in One Hundred Conservative Cases (Bilateral Gangrene, New England Deaconess Hospital, 1923-1930)*

Gangrene of other foot	41
Average interval from discharge to onset	24.7 months
Average age at first operation	63.2 years
Average duration of life after first operation*	73.8 months

* Four patients are still living and therefore are not counted

without operation have died. In table 5 are listed conditions which, in our judgment, were responsible for the deaths of these patients. Our early insistence that amputation, once definitely indicated, must be done with a minimum of delay if the patient is to remain in the hospital has done much to minimize the number of patients dying of infection. However, introduction of the guillotine amputation in 1927 and gradual extension of the indications for its use during the next few years have been largely responsible for maintaining the mortality from infection at consistently less than 5 per cent during the past six years (chart 1). Our greatest problem is still presented by the deaths, many of them sudden

which are due to degenerative changes in the heart and arteries, to pulmonary embolism or to sepsis and disease of the urinary tract

Late Results—The first 100 consecutive patients to leave the hospital after major amputations for gangrene have been followed carefully (table 6). Early cases have been selected for this study, because only when all of the patients are dead can their disease be truly understood. Four of the 7 patients known to be living have had double amputations,

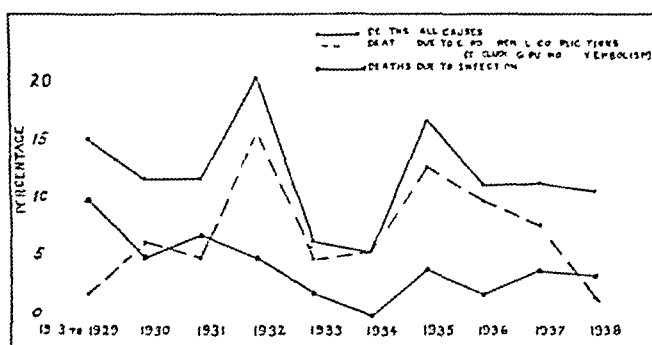


Chart 1—Yearly mortality from 1923 to 1939, showing the variation from year to year and the relative importance of cardiovascular conditions and infection

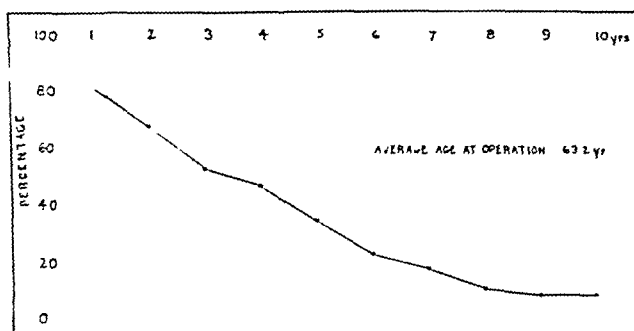


Chart 2—Survival rate for 92 consecutive patients who died after amputation for gangrene

1 patient is untraced. The others are dead. Fifty-five per cent of these patients were alive at the end of three years, and only 37 per cent were living five years after operation (chart 2). The average postoperative duration of life for the 92 patients who died was forty-four and one-half months. Forty-one per cent have had either gangrene of the other extremity, which was a factor in their death, or an amputation of the remaining leg (table 7). The average interval between discharge from the hospital and onset of gangrene on the other side was twenty-seven and seven-tenths months. It is of interest that the average postoperative

duration of life of the patients who died after a single amputation was thirty-seven and one-half months, while for patients who are dead at the time of writing but who had bilateral amputations it was seventy-three and three-tenths months

This study and our experience with amputation of the remaining leg for gangrene suggest that the incidence of bilateral gangrene in diabetic patients who have had one leg removed for obliterative arterial disease is about 40 per cent, that the mortality of the first amputation is nearly twice that of the second and that patients who accept bilateral amputation may look forward to nearly twice the life expectancy of the others

The physical as well as the economic future of the diabetic patient who has had an amputation for gangrene is not pleasant to contemplate. These as well as the immediate hazards of the disease should be kept constantly before the surgeon as a stimulus to simplify the management of these patients and to minimize the duration of hospitalization

Refusal of Operation—As has been stated, it has been our policy to insist on the discharge from the hospital of any patient with gangrene who refuses operation when in the judgment of our group amputation seems indicated. Realizing the seriousness of such a policy, we have followed carefully all patients who have left the hospital against advice. In several instances the trails of these patients seeking relief had to be followed to various cities in New England and not infrequently to New York city. When one realizes that in the thirteen years prior to Jan 1, 1939, only 33 patients have refused amputation, one cannot but be impressed with the confidence which group discussion and group study inspire in a patient.

The end result is known for all of the 33 cases.¹¹ Eleven patients survived later amputation of the extremity, 20 died either of progressive gangrene or after amputation elsewhere, 1 had slow healing but has never been able to walk on his foot, 1, who does not strictly belong to this group but is included because amputation was recommended as the procedure of choice, had gradual healing and died four years later of coronary thrombosis. I only wish it were possible to include data on the financial sacrifice made by the families of these unfortunate persons in their vain endeavor to accomplish the impossible.

SUMMARY

The organization at the New England Deaconess Hospital for the care of patients with diabetes mellitus and a gangrenous lesion of an extremity is described.

11 Twenty-five of the 33 patients were women

Nine hundred and seventy-two cases of obliterative vascular disease in patients with diabetes mellitus are reviewed

The sex distribution was about equal The average age was 64.3 years The average duration of diabetes was eight and seven-tenths years The mortality in the hospital was 9.4 per cent The mortality after major amputation was 13.9 per cent

The causes of death in 73 fatal cases are discussed

A comparison is given of the results following the use of silk and catgut sutures in 112 consecutive primary supracondylar amputations

One hundred consecutive patients who left the hospital after a major amputation for gangrene have been followed The incidence of gangrene of the other extremity, the survival rates and the average postoperative duration of life are given

The end results in the cases of 33 patients who left the hospital after refusing amputation are given

RECENT ADVANCES IN ANESTHESIA—1939

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With the passing of each successive year, many additions to the rapidly expanding field of anesthesia are made. The past year has added its share of developments. Although there has been but slight advance in the development of new anesthetic agents which are superior to older agents, valuable advances in the use and application of older agents and methods have been made. With inhalation and regional anesthesia still holding their place among the standard methods, intravenous anesthesia has made a progressive advance. Its increased usefulness has been apparent throughout the United States, and its promising possibilities are being fulfilled. Advances in local, spinal, inhalation and intravenous anesthesia will be considered individually, but before this is done a consideration of other methods is in order.

Rectal anesthesia still holds a place in selected cases, but its use is not as prominent as heretofore. Ether in olive oil is still much employed for obstetric anesthesia and analgesia but is now little used in general surgery. Tribromethyl alcohol in amylene hydrate (avertin with amylene hydrate) is still extensively employed as a basal rectal anesthetic and fills a useful place. However, to be thoroughly safe it should be used only to produce basal narcosis and not as the sole anesthetic agent. Many anesthetists prefer to administer one of the barbiturates orally, rectally or intravenously for preanesthetic medication in preference to other, more complicated basal anesthetic agents administered by rectum.

As young children possess a relatively high tolerance to the rectal administration of tribromethyl alcohol in amylene hydrate (avertin with amylene hydrate), the use of this anesthetic is often of advantage. This is true particularly in certain operations and manipulations about the respiratory passages. As an example, one may cite the removal of a foreign body from the trachea or esophagus of a young child. The rectal administration of this agent usually produces sufficient anesthesia for completion of the procedure. Too deep a narcosis is not desirable.

From the Section on Anesthesia, the Mayo Clinic

and it is safer to maintain the pharyngeal and laryngeal reflexes to a certain degree. The average dose ranges between 80 and 100 mg per kilogram of body weight, the dose may be increased slightly if the child is particularly robust. The solution should be instilled about ten minutes prior to the manipulation. The fact that the child is not completely relaxed and may cough or strain at times is not of particular disadvantage to the surgeon, when these signs are present the child will barely be overdepressed. Equipment for administration of oxygen and for maintenance of a free airway should always be available.

The barbiturates continue to be useful as basal narcotics for rectal administration. When persistent vomiting is present or when the patient is psychotic and refuses medication by mouth, the rectal route may be employed. A longer-acting barbiturate, such as sodium amytal (sodium isoamylethylbarbiturate), is preferable if prolonged sedation is desired, if a shorter period of sedation is required, pentobarbital sodium or one of the shorter-acting barbiturates will be adequate. One of the shorter-acting barbiturates will be more desirable for use as a preanesthetic medicament. The rectal method of administering barbiturates is particularly useful for the sedation of young children. Pentobarbital sodium administered half an hour prior to the giving of a blood transfusion to a child renders him quiet and amenable to the procedure. Usually he will rouse only during the venipuncture, and he will sleep quietly during the infusion. Such sedation makes administration of a transfusion to an infant or a young child much easier to accomplish, and the child seldom remembers the occurrence. Children tolerate pentobarbital sodium well, and those as young as 1 year of age may be given $1\frac{1}{2}$ grains (0.1 Gm). If there is any doubt as to the amount to employ, a smaller dose—for example, $\frac{1}{2}$ grain (0.032 Gm)—should be given and repeated until the desired effect is obtained. The easiest method of administering pentobarbital sodium by rectum is in a capsule, which should be punctured several times with a pin prior to insertion to hasten solution and absorption. If desired, a solution of the drug may be made up and instilled into the rectum or the drug may be administered in the form of a suppository.

Adequate preliminary medication is essential prior to inhalation, local, spinal or intravenous anesthesia. The agents still most frequently employed for this purpose are morphine and atropine administered subcutaneously and a barbiturate administered orally, rectally or intravenously. Some physicians prefer to employ scopolamine instead

of atropine. Premedication is begun the night before operation, at this time, $1\frac{1}{2}$ grains (0.1 Gm) of pentobarbital sodium is administered orally. The following morning an additional $1\frac{1}{2}$ to 3 grains (0.1 to 0.2 Gm) of pentobarbital sodium is administered by mouth about an hour and a half before the operation. One half to three quarters of an hour before the operation, $\frac{1}{6}$ grain (0.01 Gm) of morphine sulfate and $\frac{1}{150}$ grain (0.00043 Gm) of atropine sulfate are given by hypodermic injection. The dose of the various agents will vary with each patient, depending on the degree of excitability and on whether or not the condition of the patient contraindicates the use of one or more of the agents.

Endotracheal intubation becomes more and more useful as time goes on, both as an adjunct to anesthesia and for purposes of resuscitation. The Magill type of curved, soft rubber catheter continues to be the apparatus of choice. For resuscitation, a rigid or semirigid tube may have advantages in certain cases in which intubation is difficult, or the Magill tube may be inserted by means of an obturator to give the endotracheal catheter added rigidity. Catheters with inflatable cuffs are used in certain instances (for example, in some intrathoracic operations) and when a leakproof system cannot be otherwise maintained. Ordinarily, this may be accomplished by means of a moist or petrolatum gauze pack placed firmly in the oropharynx, around the endotracheal catheter. Endotracheal intubation is not performed routinely in general surgical procedures with inhalation anesthesia but is reserved for use in cases in which a free airway may not be otherwise obtained. Intubation is most frequently carried out prior to the beginning of the operation if the proposed procedure is on the upper part of the abdomen, if it is to be long or extensive or if the patient is frankly a poor risk and complications are anticipated. Most intracranial operations and extensive operations about the head and neck continue to be performed under endotracheal anesthesia.

Pyrex glass tubes, formerly used to protect the endotracheal catheters and maintain them in a clean or sterile condition, have been superseded by transparent, unbreakable plastic cases curved to the shape of the catheter. Whether both the endotracheal catheters and their plastic cases are to be maintained in a sterile condition is a matter of individual preference. In any event, the casing serves the purpose, protects the catheter from any gross contamination after it has been boiled, protects it from injury and prolongs its life. These plastic cases are light and durable and seldom need to be replaced. Although they are not resistant to boiling, to autoclaving or to the action of sterilizing agents containing

alcohol, they may be safely sterilized in aqueous solutions of metaphen (the anhydride of 4-nitro-5-hydroxymercuriothiosol) or merthiolate (sodium ethylmercurithiosalicylate)

INTRAVENOUS ANESTHESIA

Although no new agents possessing outstanding merit as intravenous anesthetics have been evolved during the past year, certain improvements and advances have been made in the method of administration and scope of the agents already in use. The most reliable and satisfactory agents in use at present for this purpose, as has been previously reported, are the short-acting barbiturates pentothal sodium (sodium ethyl-1-methyl-butyl thiobarbituric acid) and evipal sodium (sodium n-methyl-c-c-cyclohexanolmethyl barbituric acid). Both produce effective and satisfactory anesthesia when administered by the fractional method of injection. Their use is safe only in the hands of competent anesthetists who are aware of the dangers and contraindications. The technic of administration, the effects and the scope of action of these two agents run parallel, and each fills a useful place. Pentothal sodium is the more potent of the two, it produces better anesthesia, and somewhat smaller doses are required. One of the most important advances in intravenous anesthesia is the reduction in concentration of the solution to be injected. During the past few years the concentration has been reduced from 10 per cent to 5 per cent, and it has now been further reduced to 2.5 per cent. This concentration is felt to be the optimum for a number of reasons. Since pentothal sodium in 2.5 per cent solution has been employed, the incidence of delayed phlebitis has been reduced to practically nil, as has that of other forms of venous irritation following its use. Should extravascular injection of such a dilute solution occur, the irritating effect on the tissues would be slight and transient. Although a larger volume of solution must be injected than would be necessary if a more concentrated solution were employed, the resultant anesthesia is just as effective. With use of a 2.5 per cent solution, smaller total doses have seemed to be employed, and there is less tendency, particularly for the beginner, to give larger doses than are actually required. Thus, a wider margin of safety is attained.

The scope of intravenous anesthesia has also been widening, and the types of operation for which it may be used to advantage have increased. The fact that it is a method which excludes the hazard of fire and explosion is one factor which accounts for its increasing use. Improved methods of administration are another. Minor operations in all fields of general and special types of surgery have been performed

for some years with the use of intravenous anesthesia, longer and more extensive operations are now being done. This has been accomplished largely through the use of suitable supplementation of the intravenous method. Local and regional anesthesia, which has been employed for some time for this purpose, reduces the amount of the barbiturate necessary to produce satisfactory anesthesia. Certain abdominal operations may be performed with safety by using such a combination.

Intravenous anesthesia is increasing as a supplement to spinal anesthesia when the latter is inadequate or is beginning to wear off or when nausea or straining is present. It is well to inject the barbiturate very slowly and cautiously if the patient has been given a spinal anesthetic, otherwise, overdepression of a respiratory function already depressed by the spinal anesthetic may result.

In certain cases even excessive amounts of the barbiturate fail to produce adequate anesthesia. It is unwise to continue giving such large doses. Lundy has suggested intravenous administration of morphine as a supplement in such instances. The syringe containing the barbiturate is removed from the intravenous needle, which is left in the vein. A syringe containing $\frac{1}{6}$ gram (0.01 Gm.) of morphine sulfate in 3 cc. of physiologic solution of sodium chloride is attached to the needle, and small fractional doses of the morphine are administered. Throughout the injection the patient is carefully watched for signs of an untoward effect. The dose administered depends on the condition of the patient and the reactions observed. It may vary from $\frac{1}{24}$ to $\frac{1}{6}$ grain (0.0027 to 0.01 Gm.). On completion of the injection of morphine, the syringe containing the barbiturate solution is again attached to the needle, and administration of the latter drug is continued. The usual result is that the patient reacts favorably to subsequent doses of the barbiturate, and average doses then produce adequate anesthesia.

Administration of oxygen from the gas machine during induction of intravenous anesthesia permits the carrying out of more extensive operations than could otherwise be safely accomplished. This is especially true of certain abdominal operations. The effect of the oxygen is toward better relaxation when less of the barbiturate is used. Cyanosis caused by respiratory depression does not occur unless the airway becomes obstructed. The use of oxygen permits better minute to minute control and the movements of the breathing bag provide information in regard to respiratory exchange. Such a method also permits the addition of nitrogen monoxide to the oxygen for patients who require a large amount of the barbiturate. Administration of 50 to 70 per cent nitrogen

monoxide in oxygen to patients of this type materially decreases the total amount of intravenous anesthetic necessary without increasing the danger of anoxia. This combination is 100 per cent fireproof and explosion-proof and permits the free use of the cautery, diathermy or other electric apparatus. Even with these supplements, extensive abdominal operations with intravenous anesthesia are hardly justified.

The use of intravenous anesthesia for certain types of operations on the larynx has proved to be another advancement. In the past, operations for lesions on or about the vocal cords with the use of direct laryngoscopic procedures were performed with the patient under deep ether anesthesia. Intravenous anesthesia was felt to be contraindicated. Ether anesthesia, although satisfactory, carried with it certain disadvantages. To obliterate the laryngeal reflexes the anesthesia had to be carried to a deep plane, necessitating the use of large quantities of ether. As a result, the period of recovery was prolonged and there was much nausea and vomiting. This was out of proportion to the duration of the operation, which often takes only a few minutes. Certain modifications in the technic of intravenous anesthesia are necessary to the successful handling of patients by this method. Before the patient is placed on the operating table, the pharynx and the region of the glottis and epiglottis are thoroughly cocaineized by topical application of a 10 per cent solution of cocaine hydrochloride until the reflexes are obliterated. As soon as induction of intravenous anesthesia is complete, the glottis is visualized, and further cocaineization of the vocal cords is carried out if necessary. Before the operation is begun, a pharyngeal tube is passed by the nasal route and is connected to the gas machine for the purpose of delivering oxygen intrapharyngeally to the patient. With such a sequence it is not necessary to maintain too deep a plane of anesthesia. Ether presents some fire hazard, as the electrocautery is used frequently in the treatment of lesions in this region. This danger is completely excluded by the use of intravenous anesthesia. The period of recovery is shortened, and the patient is saved much postoperative discomfort. The tendency to postoperative pulmonary complications is lessened.

Bronchoscopic or esophagosopic examination of certain nervous and apprehensive patients may be performed in a similar manner. The chief variation in technic is that after induction of anesthesia and introduction of the instrument, administration of the anesthetic agent is discontinued, and additional doses seldom are required. The patient may attempt to cough and strain, but this is of little moment to the surgeon, who is accustomed to working under such conditions. As a result of

this technic, the patient is reacting vigorously by the time the examination is complete and is able to cough up blood, pus or mucus which might otherwise cause obstruction. On the other hand, if deep anesthesia is maintained throughout the operation, mechanical obstruction to respiration may follow removal of the laryngoscope, this is abetted by the loss of stimulus to the laryngeal reflexes following removal of the instrument.

Such procedures are highly technical, and the use of intravenous anesthesia for them is safe only in the hands of anesthetists who are widely experienced in these specialized methods.

The importance of intravenous anesthesia in military surgery has never been as fully realized as at present. The ease of transporting the simple equipment required adds to the value of the method. As the solutions are relatively stable for periods ranging from twenty-four to forty-eight hours provided they are not exposed to light and air for prolonged periods, sufficient solution for several administrations may be made up in a 500 cc. bottle equipped with a sterile rubber stopper. Syringes may be filled as needed by piercing the stopper with a suitable needle.

INHALATION ANESTHESIA

Inhalation anesthetic agents and methods have shown little change during the past year. Despite advances in other fields of anesthesia inhalation methods continue to be of major importance. Ether remains as useful as ever and continues to hold its place as the safest anesthetic for general administration. Although ether is now administered largely by means of the gas machine in combination with oxygen and other gases, the usefulness of the drop method should not be overlooked. This method still has wide application, owing to its simplicity and its safety, particularly in the hands of surgeons of limited experience. Divinyl ether and ethyl chloride still enjoy a limited field of application in some sections of the United States. Among the gaseous agents nitrogen monoxide, ethylene and cyclopropane all continue to be extensively employed. The carbon dioxide absorption technic of administering these agents with oxygen and with or without the addition of ether remains in almost universal use. The reliability of nitrogen monoxide for induction followed by administration of ether by the closed method is attested by the high percentage of cases in which this method is employed. Of the three aforementioned gaseous anesthetic agents nitrogen monoxide only is nonexplosive. In the light of the anesthetic explosions that have occurred in the past year in cases in which cyclopropane was being used, many anesthetists have adopted a conservative

attitude toward its use. Most of these explosions have been attributed to ignition of the explosive mixture by electrostatic spark. Many different attitudes in regard to the use of cyclopropane have arisen from these occurrences. Some anesthetists continue to employ it as previously, others, while continuing to use it, have adopted methods of electric intercoupling of the anesthetists, the patient, the gas machine and the operating table to disseminate accumulated electrostatic charges, and still others feel that its use should be limited to cases in which it is definitely indicated. Those who favor the last-mentioned practice do not keep a tank of cyclopropane on the gas machine but place the tank on the machine for use only during the duration of anesthesia in the selected cases.

Examples of suitable procedures might include operations for intra-thoracic tumors, lobectomy or pneumonectomy and operations for diaphragmatic hernia. This agent may be used also in certain cases of infection of the respiratory tract in which inhalation anesthesia appears to be indicated. Cardiac irregularities occurring in the course of cyclopropane anesthesia have received more attention in recent months than formerly. Cyclopropane is of definite value in certain cases, but its dangers must always be borne in mind.

LOCAL, REGIONAL AND SPINAL ANESTHESIA

Procaine hydrochloride continues to head the list of local anesthetic agents owing to its comparatively low toxicity and wide margin of safety. This applies to all forms of local and regional, including spinal, anesthesia. The use of metycaine, among other local anesthetic agents, continues to increase. Its longer duration of action, dose for dose, as compared with procaine hydrochloride often makes it the agent of choice for the blocking of nerve trunks and plexuses as well as for producing spinal anesthesia for operations lasting more than forty-five minutes. As the technic of its administration is identical with that of procaine except for a 10 to 20 per cent reduction in the dose, it serves as a valuable alternative local and spinal anesthetic agent for robust persons. Pontocaine hydrochloride continues to be favored by some physicians as a spinal anesthetic for prolonged operations on the lower part of the abdomen and on the pelvis. Certain workers combine dextrose with pontocaine hydrochloride to aid in controlling the level of anesthesia. The use of peridural anesthesia remains limited, and the results obtained with this type of anesthesia cannot yet be said to be consistent and reliable.

Local anesthesia has been employed as a supplement to intravenous anesthesia to the advantage of both methods, and by the use of such a combination the scope of both methods has been broadened. Standard blocks, such as sacral block, cervical block, block of the brachial plexus and paravertebral block, are employed as frequently as in the past, although intravenous anesthesia now supplants regional anesthesia in certain cases or is used to supplement the latter method. The use of diagnostic and therapeutic nerve block appears to be generally on the increase.

Spinal anesthesia would appear to have become adjusted to its level of usefulness. While some surgeons continue to favor its use for operations on the upper part of the abdomen, it is employed more often for operations on the lower part. The lower the level of spinal anesthesia required, the safer the method becomes. Ephedrine continues to be widely used for vasopressor purposes. The usual dose of ephedrine is 25 mg administered prior to the injection of the spinal anesthetic agent. Should an additional dose be required, intravenous administration is to be preferred, as subcutaneous or intramuscular administration produces an inadequate effect. Neo-synephrin hydrochloride continues to be promising as a vasopressor agent in spinal anesthesia.

Introductory Note

SYMPOSIUM ON PROTRUDED INTERVERTEBRAL DISKS

This group of papers on protrusion of intervertebral disks is presented in an attempt to bring up to date the knowledge of this definite pathologic and anatomic condition, which has in years past for the most part gone unrecognized and which results in untold suffering and accounts for a tremendous economic loss because of the incapacity of persons so affected

These papers are not a collective study, for there has been no pooling of statistics and each author has been requested to write from his own experience and to state the conclusions which he has reached with regard to this intriguing, important and timely problem

J GRAFTON LOVE, M D

NEUROLOGIC PICTURE OF HERNIATIONS OF THE NUCLEUS PULPOSUS IN THE LOWER PART OF THE LUMBAR REGION

R GLEN SPURLING, M D

AND

EVERETT G GRANTHAM, M D

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In June 1939, one of us (R G S) in collaboration with Bradford¹ suggested a group of criteria that could be relied on in the clinical diagnosis of a herniated nucleus pulposus at the fourth or fifth lumbar interspace. These criteria were based on a series of 10 cases in which surgical procedures were done without the aid of contrast myelography. Now, after a larger experience, we are reporting on the success of these criteria and amplifying those points which have been shown to be of the greatest importance in diagnosis.

We have avoided the term "protruded intervertebral disk" because we do not consider that it accurately designates the pathologic process in many cases. In order for the disk to produce symptoms we believe the annulus fibrosus must have been ruptured or torn, and if the nucleus pulposus is extruded through the tear a certain group of symptoms will usually appear, if the nucleus is not so extruded, however, another set of symptoms will be encountered. Therefore, we shall use the term "rupture of the intervertebral disk," with or without herniation of the nucleus pulposus.

It cannot be emphasized too often that a history of recurrent pain low in the back and sciatic pain is not always indicative of disease of an intervertebral disk. Neoplasms within the spinal canal or along the course of the sciatic nerve, rectal or pelvic pathologic conditions and diseases of the osseous structures must be ruled out by clinical and roentgen examination before a clinical diagnosis of ruptured intervertebral disk can be made.

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1 Spurling, R G, and Bradford, F K. Neurologic Aspects of Herniated Nucleus Pulposus at the Fourth and Fifth Lumbar Interspaces, J A M A 113 2019-2022 (Dec 2) 1939.

ANATOMIC CONSIDERATIONS

A thorough knowledge of the anatomic relations in the lower lumbar portion of the spine is essential to a clear understanding of the symptoms and signs of a herniated nucleus pulposus at this level. The

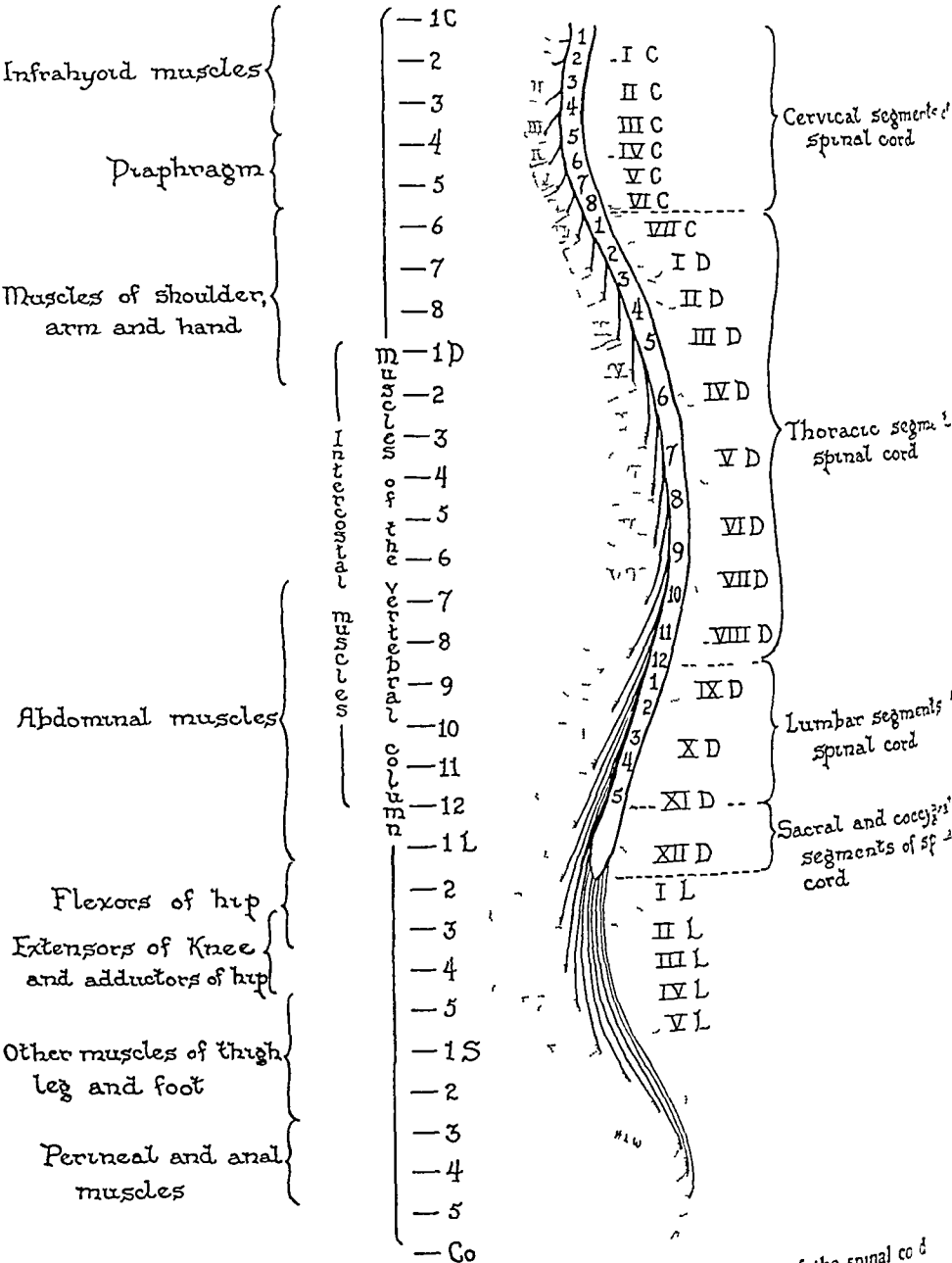


Fig 1 —Diagram showing the levels of the various segments of the spinal cord and nerve roots with reference to the vertebral column. The table at the left indicates the muscles innervated by the various roots. (From an illustration in Ran- S W Anatomy of the Nervous System, Philadelphia, W B Saunders Company, 1931)

relation of the fifth lumbar nerve to the disk between the bodies of the fourth and fifth lumbar vertebrae and the relation of the first sacral nerve to the lumbosacral disk are especially important, since over 96 per cent of ruptured disks occur at these levels

The spinal cord terminates opposite the intervertebral disk below the first lumbar vertebra (fig 1) The nerve roots of the cauda equina are freely mobile in the large lumbar canal except as they approach

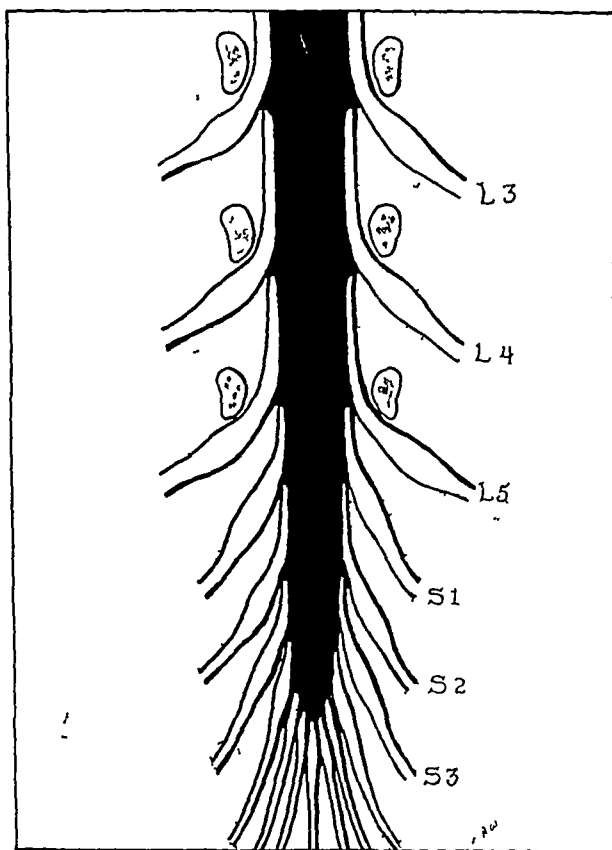


Fig 2—Diagrammatic representation of the thecal sac and the lower lumbar and sacral nerves to the pedicles and intervertebral disks of the lower part of the spine

their points of exit, where they are fixed. It is therefore apparent that only those roots that are compressed near their points of exit cause symptoms and signs of localizing value unless the lesion is a tremendously large one that compresses uniformly the roots of the cauda equina. At the level of the fourth intervertebral space the fifth lumbar nerve lies in the subarachnoid space, fixed laterally against the dura. The dural sleeve of the fifth lumbar nerve below the level of the fourth

lumbar interspace passes downward beneath the pedicle of the fifth lumbar vertebra through the intervertebral foramen (fig 2). The same relations exist between all the lumbar nerves and their respective disks. In contrast, the dural sleeve of the first sacral nerve separates from the thecal sac above the lumbosacral disk and can thus be compressed without deforming the sac. A laterally placed lesion of the fourth disk, therefore, would first compress the fifth lumbar nerve, and, furthermore, the fourth lumbar nerve could not be compressed by a lesion at this point unless it protruded into the intervertebral foramen (fig 3). Likewise, at the fifth lumbar disk the first sacral nerve is compressed first.

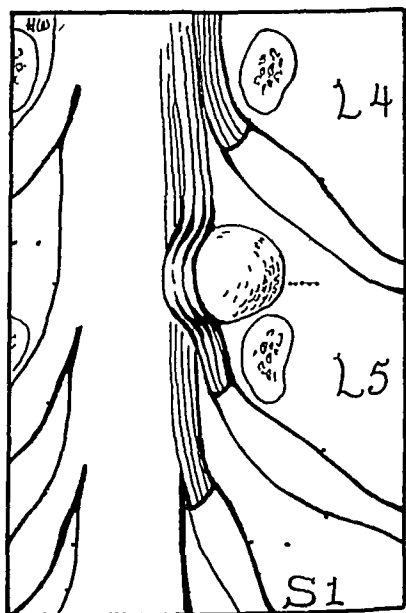


Fig 3—Diagram illustrating the mechanism of compression of the root of the fifth lumbar and first sacral nerves from a lateral herniation of the nucleus pulposus at the fourth lumbar interspace.

Most anatomic investigators have failed to demonstrate a sensory nerve supply to the intervertebral disk. It has been repeatedly shown, however, that the posterior longitudinal ligament contains a profuse supply of sensory nerves. These anatomic data have not coincided with our clinical observations, because we have repeatedly had patients who complained of pain in the back during operation with local anesthesia when the annulus fibrosus was manipulated. Consequently, Roofe undertook a reinvestigation of the innervation of the intervertebral disk.

2 Roofe, P. The Innervation of the Annulus Fibrosus and the Posterior Longitudinal Ligament at the Fourth and Fifth Lumbar Level, *Arch Neurol & Psychiat*, to be published.

and his researches have conclusively demonstrated a profuse supply of sensory nerves in the annulus fibrosus as well as in the posterior longitudinal ligament (fig 4). Furthermore, his investigations indicate that the nerve supply to the annulus fibrosus is through a recurrent branch just distal to the posterior root ganglion. After separating from the main trunk, it reenters the intervertebral foramen and supplies the liga-



Fig 4—Photomicrograph of a strand of unmyelinated nerve fibers in the annulus fibrosus. Gold chloride technic of Garvin, $\times 145$ (Roofe²)

mentous structures two vertebrae lower than the exit of the spinal nerve (fig 5). This anatomic fact sheds much light on the symptoms both in cases in which the pathologic process is limited to the ligamentous structures of the lower part of the lumbar and the lumbosacral region and in those in which a tear of the annulus fibrosus has led to herniation of the nucleus pulposus.

It is apparent from the relations just indicated that a knowledge of the exact course and distribution of the fourth and fifth lumbar and first sacral nerves, motor and sensory, is essential to a proper clinical understanding of symptoms due to lesions in these areas. In the presence of a herniated nucleus pulposus the usual finding of hypesthesia or anesthesia of the lateral aspect of the leg probably depends on combined involvement of the fifth lumbar and the first or second sacral dermatome, since involvement of a single spinal nerve rarely gives objective sensory deficit. However, paresthesias may result from involvement of a single spinal nerve. The dermatome of the fifth lumbar nerve is small, but with associated loss referable to the first sacral nerve

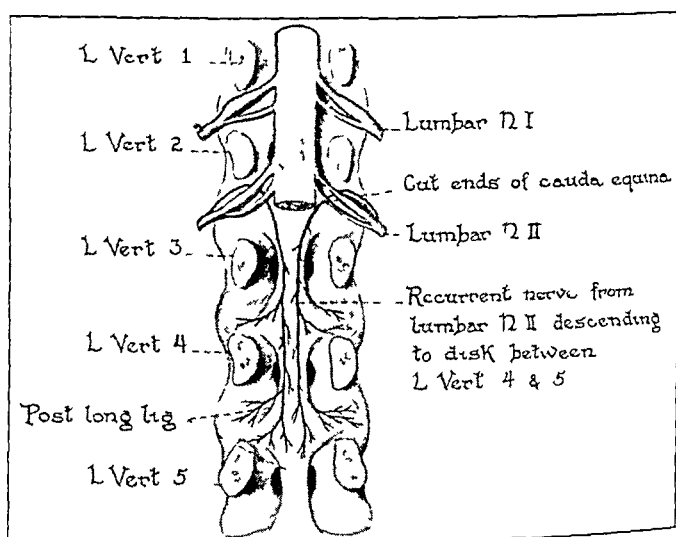


Fig 5—Distribution of the second recurrent lumbar nerve to the region of the third and fourth lumbar vertebrae and the fourth and fifth intervertebral disks (From an illustration in Spurling and Bradford¹)

there would probably be an area of hypesthesia on the anterolateral aspect of the leg. Similarly, the first and second sacral nerves would necessarily be affected to give hypesthesia or anesthesia of the more lateral aspect of the leg. The small gluteal dermatomes are rarely involved except in lesions sufficiently large to compress severely the dural sac (fig 6).

CLINICAL CONSIDERATIONS

Material Studied—The clinical data presented in this paper were accumulated from 125 consecutive laminectomies performed for intractable pain low in the back and sciatic pain. There were 92 cases of frank rupture of the annulus fibrosus with herniation of the nucleus pulposus. In the remainder of the series the final diagnosis was hyper

trophy of the ligamentum flavum in 18 cases, neoplasm in the lower lumbar canal in 4 cases and "negative exploration" in 11 cases. In a previous communication³ we have analyzed critically a cross section of the entire group. Our chief consideration here is ruptured intervertebral disk with laceration of the nucleus pulposus. This lesion occurred at the fifth lumbar interspace in 51 cases, at the fourth in 30, at the third

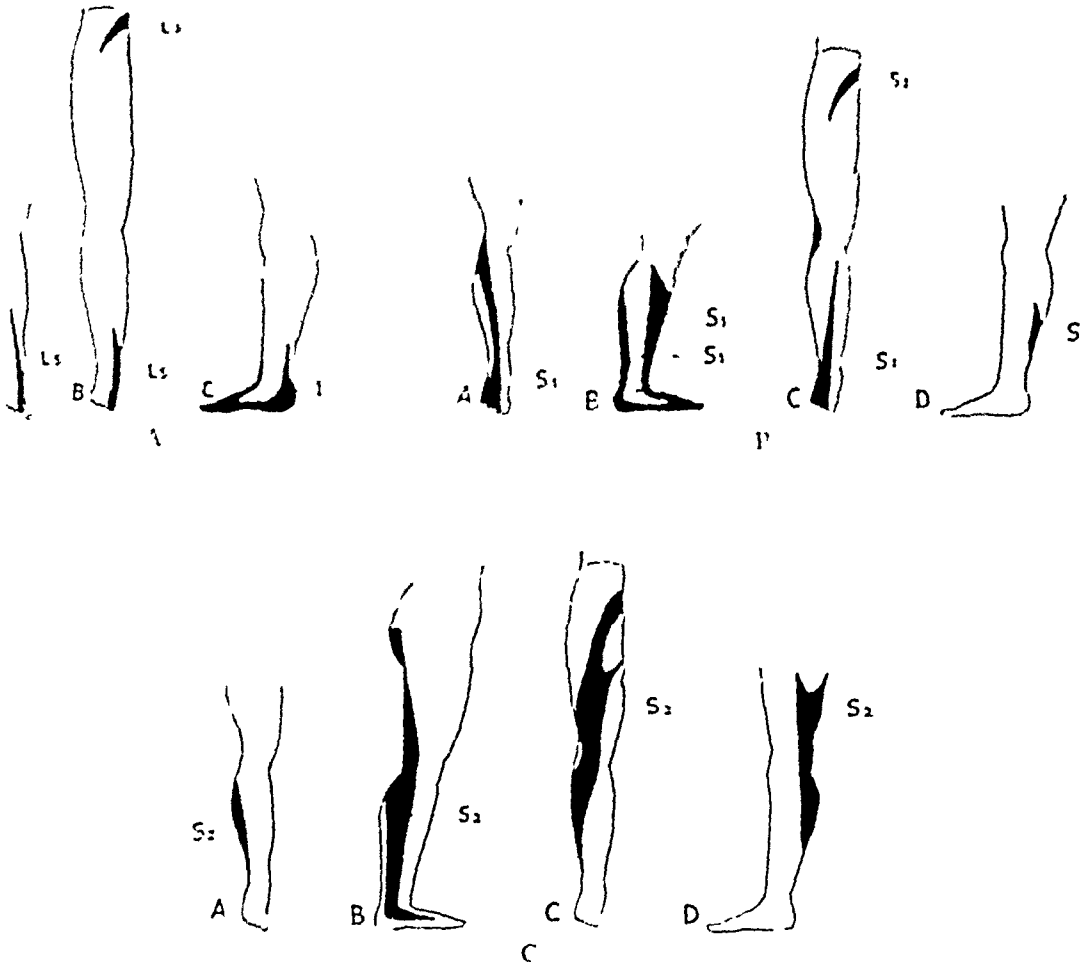


Fig. 6—Approximate dermatomes of (I) the fifth lumbar, (B) the first sacral and (C) the second sacral nerve roots. In illustration I, A represents the ventral, B the dorsal and C the lateral view. In illustrations B and C, A represents the ventral, B the lateral, C the dorsal and D the mesial view. (Modified from illustrations in Tilney, F., and Riley, H. A. *The Form and Functions of the Central Nervous System*, New York, Paul B. Hoeber, Inc., 1938. The three parts of figure 6 have been published also by Spurling and Bradford¹.)

3 Bradford, F. K., and Spurling, R. G. Intraspinal Causes of Low Back and Sacral Pain. Results in Sixty Consecutive Low Lumbar Laminectomies, *Surg., Gynec. & Obst.* 69:446 (Oct.) 1939.

in 1 and at both the fourth and the fifth in 1. The incidence, therefore, of ruptured intervertebral disk at the fourth and fifth lumbar interspaces in our series was 99 per cent.

Twenty-seven patients with this condition were subjected to operation on the basis of clinical findings alone, i. e., without the use of contrast myelography.

Symptoms—In cases of ruptured intervertebral disk an accurate history is perhaps as important in diagnosis as it is in cases of tic douloureux. The story from an observing patient may be so characteristic that not only is the probable diagnosis indicated but the exact level of the lesion can be prophesied.

The initial symptom of disease of an intervertebral disk is, almost without exception, pain low in the back (lumbago). In the absence of a definite traumatic history, the onset of acute pain in the back is usually associated with lifting in a bent-forward position or with sudden torsion of the trunk. The pain in the back may be mild or severe but in the majority of instances it is incapacitating. It is relieved only by absolute immobility, usually in a recumbent position. It is always intensified by movements affecting the spine. As the acute pain subsides and the patient becomes ambulatory, he usually finds that bending, and especially lifting in a bent-forward position, causes recurrence of the pain. The point of maximum intensity is usually the midline, but it may be to one side of the midline or may even be most severe over one or both sacroiliac articulations. Repeated attacks of "low back disability" may precede the onset of sciatic pain. However, the sciatic pain may appear shortly after the onset of the initial lumbago. As the pain in the leg increases in intensity, the pain in the back may lessen or entirely disappear. The pain in the leg may not be uniform along the course of the sciatic nerve. Points of greatest intensity are likely to be in the gluteal region, the posterior part of the thigh, the back of the knee or the lateral aspect of the leg and ankle. During the acute episode the pain both in the back and in the leg is intensified by coughing, straining or sneezing.

Paresthesias are a common accompaniment of the pain in the leg. Many patients complain of tingling, prickling, electrical shocks, coldness or numb sensations in any one of the involved dermatomes. Paresthesias below the knee in the lateral aspect of the leg or foot or in the second, third and fourth toes are characteristic of lesions at the fifth lumbar interspace. Paresthesias involving the great toe, the top of the foot and the medial aspect of the heel are characteristically associated with lesions at the fourth lumbar interspace. Paresthesias are usually not constant but appear with certain postures or on coughing, straining or sneezing.

Weakness is not usually a major complaint, but not infrequently the patients state that they favor the painful leg. In some instances, however, definite muscular weakness limited to one group of muscles is observed by the patient.

Sensory loss limited to the involved dermatomes is frequently described by an observing patient. However, in most instances paresthesias take precedence in the symptoms.

Spine—Stiffness of the lumbar portion of the spine is a prominent clinical feature but not nearly so important diagnostically as severe sciatic pain. The normal ventral lumbar curve may be completely obliterated. The absence of the curve is due to spasm of the erector spinae muscles and is especially well demonstrated when the patient bends forward. The rigidity of the lumbar portion of the spine is in no way dissimilar from that occurring in severe articular disease. Listing to one side is a common finding, the ilium usually being higher on the side of the lesion. Limitation of flexion of the lumbar portion of the spine is always present in patients who are complaining of pain in the back but may be entirely absent in patients in whom pain in the back has disappeared.

The leg-raising sign as described by Lasègue⁴ is most important in differentiating tenderness of the sciatic nerve from painful hamstring muscles. As was pointed out in the original description, patients with severe sciatica keep the knee flexed and are unwilling to put the heel on the floor, thus preventing direct tension on the nerve. The Lasègue test is performed with the patient supine. The thigh is raised until it forms a right angle with the trunk, and the leg, which has remained flexed, is extended until pain begins along the course of the sciatic nerve. Then, without further movement of the leg or thigh the foot is passively dorsiflexed to determine whether the additional pull on the sciatic nerve intensifies the pain. We believe that this test gives a positive result in all cases of herniation of the nucleus pulposus involving the components of the sciatic nerve. A modification of the Lasègue test for use in cases of severe acute sciatic pain is performed as follows. With the patient lying supine and the legs and feet outstretched, the foot is quickly dorsiflexed. Acute pain along the course of the nerve following this maneuver is indicative of irritation of the sciatic nerve.

Naffziger and Jones⁵ have described a test which we feel is of extreme importance in the diagnosis of intraspinal lesions. It is performed by occluding both jugular veins until a sense of fullness in the

⁴ Lasègue, C. Consideration sur la sciatique, *Arch. gen. de med.* 2:558, 1864.

⁵ Naffziger, H. C., and Jones, O. W. Dermoid Tumors of the Spinal Cord, *Arch. Neurol. & Psychiat.* 33:941 (May) 1935.

2 Positive Lasegue test

3 Positive Naffziger test with paresthesias involving the fifth lumbar, the first sacral and perhaps the second sacral dermatomes

4 Ankle and knee jerks uninvolved

5 Hypesthesia and paresthesias in the fifth lumbar and first sacral dermatomes

Fifth lumbar interspace

1 Disability of the lower part of the back with absence of lumbar lordosis and localized tenderness to pressure over the fifth lumbar vertebra

2 Positive Lasegue test

3 Positive Naffziger test, producing paresthesias radiating into the first and second sacral dermatomes

4 Diminution or absence of ankle jerk

5 Hypesthesia involving the first and second sacral dermatomes

COMMENT

The recurrent episodes of pain low in the back which almost invariably precede the sciatic pain of herniated nucleus pulposus are probably due to disease of the intervertebral disk and the posterior longitudinal ligament. Tearing of these structures either from frank trauma or as a result of repeated small traumas incident to weight bearing may be the only cause. Of course, the susceptibility of the disk to trauma may be due to congenital weakness or to degenerative changes in this structure. With tearing of the annulus fibrosus and the subsequent inflammatory reaction therefrom, the sensory nerve endings, with which the structure is richly supplied, are stimulated, hence the pain in the back. The pain remains localized to the back unless the tear is sufficiently large to permit extrusion of the nucleus pulposus or detached portions of the annulus fibrosus into the spinal canal. When such extrusion occurs, one or more roots of the cauda equina may be impinged on and then pain in the leg results. Whether or not demonstrable neurologic signs occur depends on the degree of compression of the nerve roots.

Many patients with injury to the annulus fibrosus and even recurrent attacks of lumbago undoubtedly recover without the development of a herniated nucleus pulposus that impinges on the nerve roots. It must be remembered, however, that the nucleus may extrude through a median rupture of the annulus fibrosus without causing root compression sufficient to produce pain in the leg. The dominant symptom in such circumstances would continue to be local pain in the back.

Tears of the annulus fibrosus apparently are more likely to occur in the posterolateral aspect, owing to the poor lateral development of the posterior longitudinal ligament, which supports the annulus fibrosus. At the third lumbar interspace such a posterolateral herniation compresses primarily the fourth lumbar nerve root just above its exit from the dural sleeve. At the fourth lumbar interspace the fifth root is thus primarily compressed. However, if the herniation occurs far lateralward at either level the root corresponding to the interspace may be compressed at the intervertebral foramen. If the herniation is large, the thecal sac may be compressed from the side, and, in addition, the lower nerve roots on the same side may be sufficiently compressed to produce a neurologic deficit. Rarely, however, is disruption of the disk sufficiently large to compress uniformly all the roots of the cauda equina, thereby producing diffuse bilateral signs.

It is the compression of one or more components of the sciatic nerve which gives rise to the severe "sciatica." From involvement of either the fourth or the fifth lumbar or the first sacral root alone, pain can occur along the entire course of the nerve. That the knee jerk may be diminished or absent with herniation at the level of the third lumbar interspace is in keeping with the accepted innervation of the quadriceps femoris muscle by the fourth and fifth lumbar nerves. That the ankle jerk is unaffected by typical herniations at the fourth lumbar interspace and is diminished or absent with herniations at the fifth lumbar interspace is also consistent with the accepted innervation of the gastrocnemius and soleus muscles by the first and second sacral nerves.

That these neurologic symptoms and signs are accurate and reliable is attested by the fact that during the past eight months we have successfully removed 26 consecutive herniations of the nucleus pulposus without confirmation with iodized oil or other contrast mediums. In the twenty-seventh case, confirmation of the clinical findings was not made at operation. In the same period we have used iodized oil in 28 cases for verification of the lesion. In this group there were 12 cases in which the clinical findings were sufficiently clearcut to justify surgical exploration without iodized oil but in which for various reasons roentgen verification was demanded. In the group in which iodized oil was used there were 4 failures of verification. In 2 cases of this group the clinical picture definitely pointed to herniation at the fifth lumbar interspace, yet the iodized oil study indicated the lesion to be at the fourth lumbar interspace. The accuracy of the clinical findings in both instances was confirmed, whereas the defects observed with iodized oil were explained only by the presence of a hypertrophied ligamentum flavum. On the basis of our experience thus far we feel much safer in subjecting patients

to operation when the clinical findings are clearcut than when an iodized oil study is necessary for accurate diagnosis

SUMMARY

1 The diagnosis of rupture of the intervertebral disk with herniation of the nucleus pulposus in the lower lumbar region can be made in many instances from clinical findings alone. In fully 50 per cent of cases, not only can the diagnosis of the lesion be made, but the exact level can be predicted accurately.

2 A careful consideration of the clinical findings is of importance not only in selecting cases for operation without contrast myelography but in making a more conservative selection of cases for the injection of iodized poppyseed oil.

3 The neurologic findings of herniated nucleus pulposus are not peculiar to this one clinical entity, since neoplasms within the spinal canal or along the course of the sciatic nerve, rectal or pelvic pathologic conditions and diseases of the osseous structures may simulate this clinical picture. The need, therefore, of a complete clinical study of all patients with disability of the lower part of the back and of the leg before contrast myelography or exploration is resorted to is apparent.

PATHOLOGY OF THE INTERVERTEBRAL DISK

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VERNE T INMAN, M D, P H D

SAN FRANCISCO

INTRODUCTION

There is a growing appreciation of the significance of the intervertebral disk in its relationship to spinal disease. When it is remembered that the disks make up a full quarter of the total length of the presacral portion of the spinal column, it is evident that these structures constitute an extensive organ. In point of fact it may be said that the greater majority of conditions resulting in spinal deformity or in derangement of spinal function are primarily the outcome of involvement of the intervertebral disks.

For a clear appreciation of the pathologic pictures and notably for the interpretation of pathologic processes and their genesis, a thorough acquaintance with the structure and function of the disks is essential. From decade to decade there are considerable variations in both the anatomic character and the physiologic competence of the disks, hence it is necessary to consider their developmental history. Nonetheless a fine distinction at any given age period between what is normal and what pathologic is often difficult to draw. It is this difficulty which emphasizes the need for examination of the disk in terms of a continuous process of change. For this point of view we are indebted to the late Professor Schmorl, of Dresden, Germany, whose work, together with that of his pupils, has served to develop what we feel to be the fundamental approach to pathologic conditions of the disk. Schmorl's pioneer effort has been the stimulus for much further investigation along such lines.

From the Department of Applied Anatomy and the Department of Orthopaedic Surgery, University of California Medical School

For a complete bibliography of the subject the reader should consult Saunders, J B de C M, and Inman, V T. The Intervertebral Disc. A Critical and Collective Review. *Internat Abstr Surg* 69 14-29 1939, in *Surg Gynec & Obst* July 1939

ANATOMIC AND HISTOLOGIC ASPECTS OF THE NORMAL DISK

The interval between each two vertebral bodies is occupied by the intervertebral fibrocartilaginous disk. The vertical thickness of each disk varies from region to region, being thinnest from the third to the

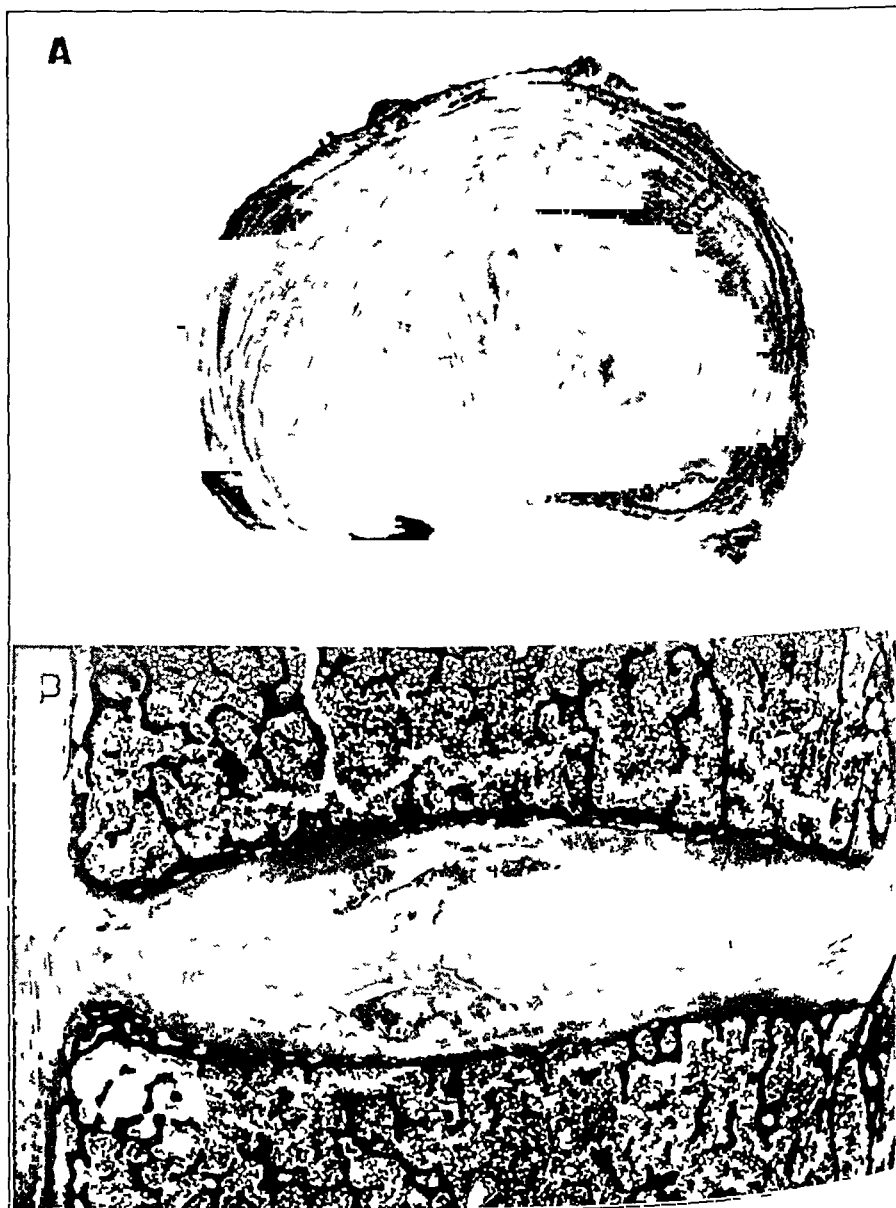


Fig 1—*A*, dissection of the cartilage plate of a lumbar vertebra. Note the central zone, through which appears the underlying bone. Peripherally its blending with annular fibers is evident. In the central zone a group of fissures filled with gelatinous scars are seen. *B*, sagittal section of a normal thoracic disk from a man aged 21. Note the three components of the disk.

seventh thoracic and thickest in the lumbar segment. Ventral and dorsal inequalities in thickness conform to and are in some measure responsible for the characteristic curves of the spinal column. The essential unit is made up of three parts: the annulus fibrosus, the nucleus pulposus and the cartilage plates. This concept of the disk as a tripartite unit is of the greatest importance for the interpretation of the various morbid processes which affect these structures.

The cartilage plates cover the end surfaces of the opposed vertebral bodies. On gross examination they are well defined centrally but disappear marginally by blending with the annulus fibrosus (fig 1A). Microscopically the plate is composed predominantly of hyaline cartilage, which is, however, definitely more fibrous at the periphery. The cells of that surface, in apposition to the bony centrum, are irregularly arranged whereas those of the internal aspect, facing the nucleus pulposus, lie for the most part parallel to the surface (fig 1B). The average plate is approximately 1 mm in thickness but is usually thinner at the center. Marginally the cartilage blends imperceptibly into the fibers of the annulus, and at this point its cellular elements tend to orient themselves in the direction of the entering fibers. The surface opposed to the bone is found unsupported at the intertrabecular intervals, where the bone marrow is found in direct contact with the cartilage plate. The internal surface is sharply delineated from the nuclear material. However, delicate fibers passing vertically from the nucleus can be discerned entering the plate by suddenly changing their axis and paralleling its surface.

The nucleus pulposus occupies approximately the center of the disk, a little nearer the posterior than the anterior aspect. The transition between nucleus and annulus is progressively more indefinite the younger the specimen. Normally the nucleus is soft and elastic, somewhat slimy to the touch, and, because of its inherent turgor, bulges on section, above the cut surface. In what may otherwise be considered a healthy disk one frequently encounters a cavity into which project villus-like processes (fig 2). This cavity has been interpreted (Luschka,¹ Schmorl²) as a rudimentary joint space. However, owing to the greater frequency with which such cavities are found in the disks of older subjects and their common appearance, apparently as an artefact, on dehydration by alcohol during the process of sectioning, we incline to the opinion that these cavities are indicative of an early degree of desiccation of the disk.

1 Luschka, H. *Die Halbgelenke des menschlichen Körpers*, Berlin, G. Reimer, 1858.

2 Schmorl, G. *Ueber die an den Wirbelbanscheiben vorkommenden Ausdehnung und Zerreissungsvorgänge und die dadurch an ihnen und der Wirbelspongiosa hervorgerufenen Veränderungen*, Verhandl d deutsch path Gesellsch 22: 250, 1927.

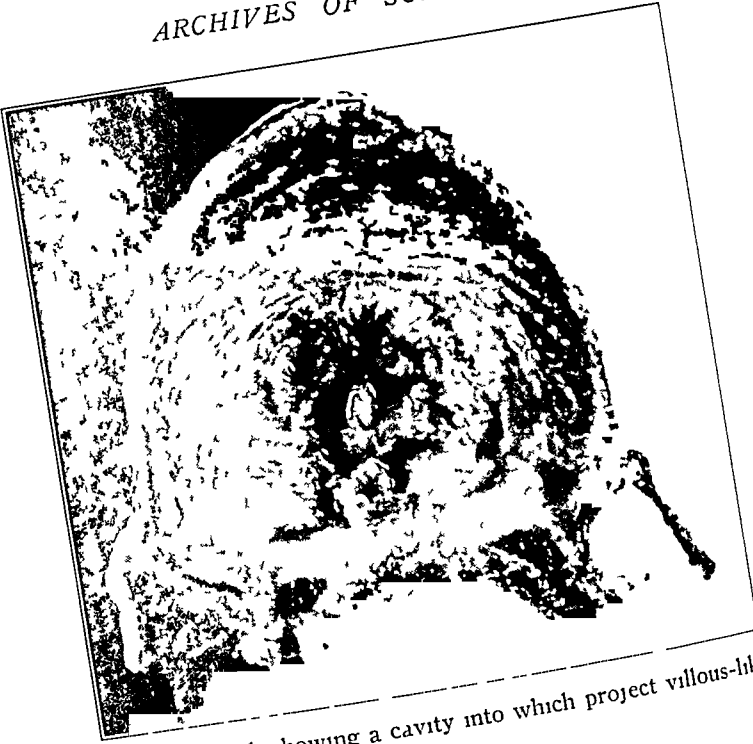


Fig 2—Thoracic disk showing a cavity into which project villous-like process. There is some degeneration in this disk.

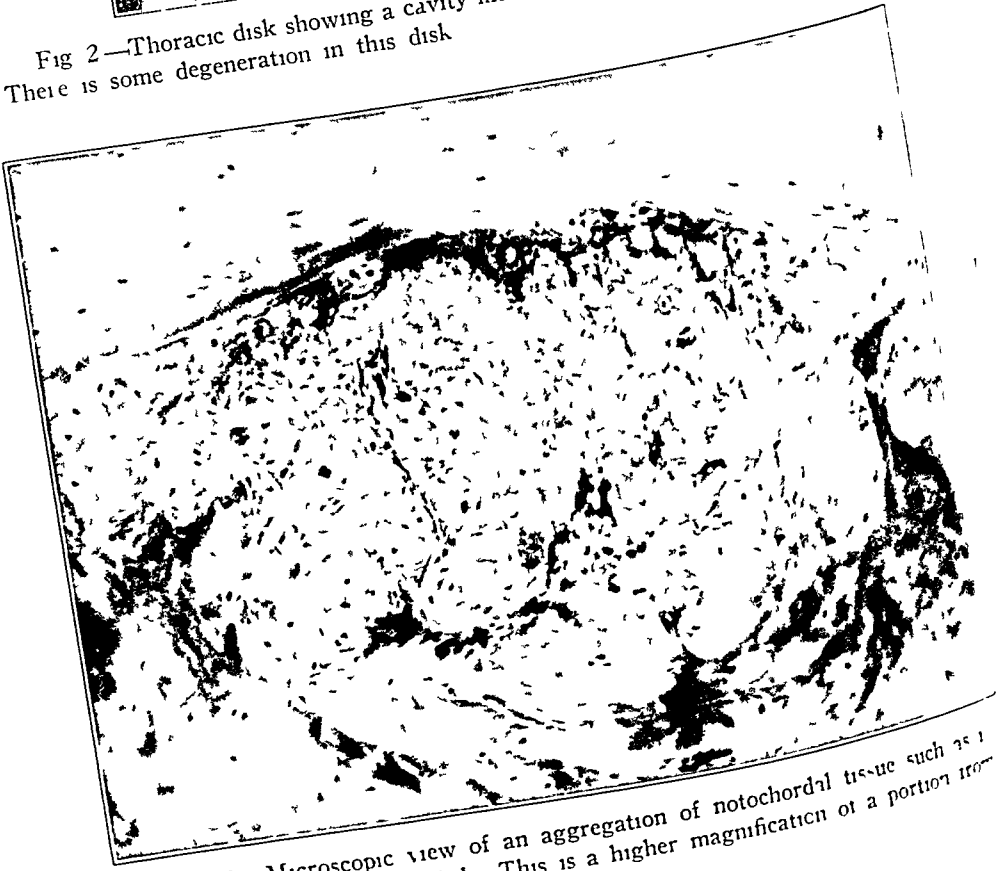


Fig 3—Microscopic view of an aggregation of notochordal tissue such as is often found in the normal disk. This is a higher magnification of a portion from the central area of figure 1 B.

Histologically the nucleus consists of a loose network of delicate fibrous strands with a variable number of cellular elements enmeshed. Centrally the arrangement tends to be highly irregular, or the ground substance may be more homogeneous and relatively structureless. Aggregations of notochordal tissue are most definite in this region (fig 3). The cells comprising these aggregations are large and occur in clumps of two or three, which are usually well differentiated from the ground substance by condensations of fibrous tissue. The cytoplasm of these cells is abundant and vacuolated. The nucleus tends to be eccentrically and is surrounded by a clear halo, about which the cytoplasm is granular. These are the so-called physaliferous cells of Virchow. Each cell, as well as the cell group, is sometimes surrounded by a concentric sheath of fibrous tissue, recalling the appearance seen in the embryonic notochord. Furthermore, these cells when viewed at low magnification are not unlike cartilage cells, for which they are frequently mistaken, but their roseate grouping is typical. Characteristically a fairly large isolated colony of these cells may be found, above and below, in juxtaposition to the cartilage plate immediately opposite its thinnest central portion. This arrangement not only emphasizes the notochordal origin of these aggregations but suggests that the thinned and somewhat depressed central area of the cartilage plate indicates the point of obliteration of the primitive notochordal canal.

In the more peripheral portion of the nucleus the delicate wavy fibers of connective tissue are more apparent. The cellular elements are few and scattered, consisting of an isolated physaliferous cell or an occasional fibroblast. The transition from nucleus to annulus is gradual and is discernible only by the increasing size of the collagenous fibers. Sections often show centrally large irregular clefts, which may contain cellular debris. We feel that in normal disks these are for the most part artefacts produced during dehydration. From our personal observations we are unable, on either macroscopic or microscopic grounds, to accept the statement that a rudimentary joint space occurs in the normal disk, as contended by Luschka,¹ Schmorl² and Smith.³

The annulus is composed of heavy collagenous bands, which become coarser as the margins of the disk are approached. The innermost fibers pass into the peripheral edges of the cartilage plate. Those intermediate in position gain attachment to the bone as the fibers of Sharpey, while the most external bundles blend with the adjacent ligaments and fibrous periosteum of the centra. As mentioned, the cellular elements in the neighborhood of the cartilage plates are for the most part cartilage cells oriented in the line of the fibers. Elsewhere mature fusiform fibroblasts predominate.

3 Smith, N. R. The Intervertebral Discs, *Brit J Surg* 18: 358, 1931.

PHYSIOLOGIC CONSIDERATIONS

The intervertebral disk plays a most important part in the functional mechanism of the spinal column. Not only does it permit movement to occur between the series of vertebral segments, but it is related to the transmission of body weight, to the absorption and dispersal of the multitudinous shocks to which the column is constantly exposed and to the maintenance of the spinal curves.

The elastic turgor of the disk exerts an expansile force on the opposed vertebral bodies, which is resisted by the various spinal ligaments, thereby establishing a state of internal equilibrium that serves both to resist deforming forces and, when deformity has occurred, to restore the column to the "status quo." This expansile force is due to the compression of the nucleus pulposus within the confines of the annulus and the cartilaginous plates and approximates in the individual disks of the lumbar region some 30 pounds (13.5 Kg). This estimate was made by Petter⁴ on fresh cadavers and on subjects in the supine position. But in the living subject when erect the superincumbent weight of the trunk and upper extremities must raise this pressure in the lower lumbar regions to well over 100 pounds (45.5 Kg). During transitory phases of spinal movement, as when the back is extended from the flexed position, even with no resistance but that of gravity, estimates would indicate that the pressure may be in excess of 200 or 300 pounds (90.5 or 135 Kg). That the disk is able to withstand pressure of such magnitude is no doubt related to its high water content. One knows from Pascal's law that liquids transmit in all directions and without diminution any pressure that is applied to them and may for all practical purposes be considered as incompressible. Uebermuth⁵ and Puschel⁶ studied the water content of the disk, and there appears to be a close correlation between the elasticity of the nucleus pulposus and its water content. Progressive desiccation appears to be a prime factor in senile destruction of the disk and the production of pathologic lesions, for a desiccated disk is an inelastic disk, little able to withstand the compressing forces to which it is constantly subjected. The disks possess a considerable affinity for water. This is simply demonstrated by examining the change which occurs in the disks of a partially dried cadaver after they have been soaked in water for a few minutes. Before immersion the cut surface of the nucleus pulposus shows no

4 Petter, C. K. Methods of Measuring the Pressure of the Intervertebral Disk, *J. Bone & Joint Surg.* **15** 365, 1932.

5 Uebermuth, H. Die Bedeutung der Altersveränderungen der menschlichen Bandscheiben für die Pathologie der Wirbelsäule, *Arch. f. klin. Chir.* **156** 667, 1929.

6 Puschel, J. Der Wassergehalt normaler und degenerierter Zwischenwirbelscheiben, *Beitr. z. path. Anat. u. z. allg. Path.* **84** 123, 1930.

elevation above the plane of section. After immersion there is a remarkable transformation in the nucleus. It rapidly regains its turgor and expands to bulge a quarter of an inch or more above the surface. The annulus, however, shows no more change than do the neighboring paravertebral soft parts.

Puschel's⁶ observation would indicate that the water content of normal disks is fairly constant in the same person. It is highest in the newborn and decreases with age, first rapidly and then more slowly. It is higher in the nucleus than in the annulus (80 per cent in the nucleus and 78 per cent in the annulus at birth). The ratio of the water content of the annulus to that of the nucleus remains approximately the same until the fifth decade, when rapid loss occurs in the nucleus, accompanied by various degenerative changes.

Daily variations of water content are suggested by the observations of de Puky.⁷ In measuring 1,200 persons between the ages of 5 and 90, he found a daily oscillation in their total heights. These variations amounted to about 1 per cent of the total height, averaging $\frac{1}{2}$ inch (1 cm) in females and $\frac{3}{4}$ inch (2 cm) in males. The younger persons showed a greater fluctuation than did the older ones. Those examined were taller in the morning, on arising, but decreased in stature during the course of the day. These fluctuations are reasonably attributed to compression and loss of turgor in the intervertebral disks.

Numerous investigators have demonstrated that the axis of movement between adjacent vertebrae over a limited range passes through the nucleus pulposus. The substance of the disk is such that any absolute change in its size is exceedingly small. Movement occurs by change in shape. In flexion there is compression of the disk anteriorly and expansion posteriorly, and during extension, anterior elongation and posterior compression. Should extension continue to the point where the spinous processes contact one another, this point of contact becomes the fulcrum and further extension leads to elongation of the entire disk with narrowing of its diameter. This alternating compression and extension of the disk produces displacement of the nucleus pulposus, posteriorly in flexion and anteriorly in extension. In lateral flexion there is slight displacement of the nucleus to the contralateral side.

In addition to the movements described, there are, during flexion, slight forward displacement of each vertebra on the one below and, during extension, slight backward displacement. This movement can readily be seen in lateral roentgenograms by observing the change in

⁷ de Puky, P. The Physiological Oscillation of the Length of the Body, *Acta orthop Scandinav* 6:338, 1935.

alignment of the vertebral bodies and the change in shape of the intervertebral foramen. In the thoracic and cervical regions there are superadded movements of rotation.

These movements, particularly those of a shearing nature, not only are expressed in the morphologic appearance of the disks at various levels, but are of considerable significance in the production of the various types of anterior and posterior fissuring of the annulus, in the pathologic displacements of the nucleus and in the deformities of the spine, such as scoliosis, which attend disk degeneration.

DEVELOPMENT AND MALFORMATION

The intervertebral disks have origin in part from the remnants of the primitive notochord and in part from the mesoderm between the successive blocks of rapidly chondrifying tissue which establish the true vertebral segments. The nucleus pulposus is derived at first from notochord but is extended by a mucoid change which occurs in the surrounding tissue of the so-called notochordal sheath, together with multiplication of the original chordal cells. In the last two or three months before birth there is a dispersal of the cellular groups together with the appearance of fibrocartilaginous elements from the peripherally differentiating annulus. It has been contended in contradistinction to the foregoing statements that the extension of the nucleus is at the expense of the annulus, the chorda cells disappearing completely before birth. We cannot support this contention. We have not infrequently found in adult life notochordal elements enjoying their primitive arrangement within a sheath.

The annulus differentiates later than the nucleus into fibrocartilage. The progressive development and thickening of bundles extend well into the postnatal period. Further postnatal changes are discussed with the pathologic process.

The disk is vascularized during the fetal period. This aspect has been studied in great detail by Boehmig⁸ and Uebermuth.⁹ The vessels of the disk are divided from those laying down the ossific centers of the vertebral bodies. Six groups, three from either side, are described as piercing the cartilage plates and entering the disk. These vessels, however, undergo progressive postnatal regression and atrophy, a process which leaves behind scars and faults in the cartilage plates (fig 1A).

In the opinion of these authors such defects are predisposing factors leading to fissuring of the plate and escape of nuclear material. The

⁸ Boehmig, R. Die Blutversorgung der Wirbelbandscheiben, das Verhalten des intervertebralen Chordasegments und die Bedeutung beider für die Bandscheibendegeneration, *Arch f klin Chir* 158 374, 1930.

notochordal canal is also of importance in offering an explanation of such herniations. That portion of the notochord passing through the center of the vertebral body is early transformed into a relatively cell-free ligament and, together with its canal, is obliterated during chondrification and ossification of the centrum. It may persist, leave defects or weaken the cartilage plate, allowing the hernias seen in juvenile kyphosis. More complete persistence of the canal, though rare, occurs. Persistence over several segments is most common in the thoracic region and is usually associated with malformation of the vertebral bodies and some degree of kyphosis. The "butterfly" vertebrae of Sereghy⁹ have been interpreted on this basis. Beadle¹⁰ recorded examples from the Schmorl collection of persistence of the canal, together with instances of dorsal and lateral displacement of embryonic chordal tissue, which might be interpreted in the light of Minot's¹¹ work on such displacements as they occur in animals.

Gross malformation of the disks is associated with a wide variety of congenital anomalies of the spine, such as spina bifida anterior, hemivertebrae and the Klippel-Feil syndrome. Complete absence of the disk has been described in the otherwise normal spine. Schmorl and Junghanns¹² pointed out that in examples of what they term *Blockwirbel* they found vertebrae equal in height to two vertebrae together with the disk and that study of such specimens often revealed small remnants of the disk which could not be detected in the roentgenogram. Suppression of the disk from pathologic processes as in figure 4 must be ruled out before making a diagnosis of congenital absence.

GENERAL PATHOLOGIC OBSERVATIONS

Throughout life the intervertebral disks are subject to continuous and progressive changes of structure of a character so marked as to make it difficult to determine what is normal and what is pathologic. Degenerative phenomena are so frequent in supposedly healthy spinal columns at middle age that the changes must be regarded for the most part as the outcome of age processes in an organ subjected to destruc-

9 Sereghy, M. Eine sonderbare kongenitale Missbildung (Schmetterlingsform) der 3 Lumbalwirbels. Ein Beitrag zur Frage der Entwicklung der Wirbelkörper, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **36** 353, 1927.

10 Beadle, O. A. The Intervertebral Discs. Observations on Their Normal and Morbid Anatomy in Relation to Certain Spinal Deformities, Medical Research Council, Special Report Series, no. 161, London, His Majesty's Stationery Office, 1931.

11 Minot, C. S. The Segmental Flexures of the Notochord, *Anat. Rec.* **1** 42, 1906.

12 Schmorl, G., and Junghanns, J. Die gesunde und kranke Wirbelsäule im Röntgenbild, Leipzig, Georg Thieme, 1932.

tive forces of considerable magnitude as represented by functional activity. We have already pointed out under physiologic considerations the important observations of Puschel⁶ and Uebermuth⁵ with regard to the progressive desiccation of the disk with advancing age. The commonest morbid changes found would seem to be related to such desiccation occurring prematurely or to an excessive degree. These

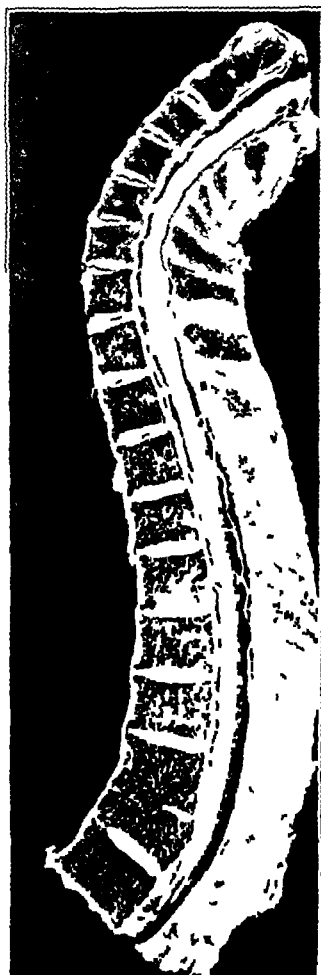


Fig. 4—Sagittal section of the cervicothoracic portion of the spinal column, showing senile kyphosis. Note particularly the anterior destruction of the disks and the corresponding sclerosis of the adjacent vertebral bony margins. In one instance there has been almost complete replacement of the disk by bone. Otherwise the disks are relatively intact.

changes are by no means equally distributed throughout the spine nor do they necessarily follow any definite rule. It is our impression, however, that at their inception they are met with more frequently in the midthoracic and lower lumbar regions than elsewhere.

The causal factors in pathologic changes of the disk are often uncertain and whether they are in their initiation physiologic degenerative, traumatic or inflammatory, they are for the most part not very dissimilar in nature, varying perhaps mostly in the degree of repair shown by such a relatively avascular structure. Whereas it should be firmly kept in mind that the unit comprising the disk consists of an annulus, a nucleus and cartilage plates, functionally depending on all elements remaining intact, we have found it convenient from a descriptive point of view to consider the pathologic appearance of these elements *seriatim*.

The cartilage plates, enclosing the nucleus, would seem to constitute the part of the disk most resistant to degenerative phenomena. They are, however of the greatest importance, in that solution in their continuity allows escape of nuclear material with consequent loss in elasticity and degeneration of the disk as a whole. This has been shown experimentally to occur in dogs, monkeys and rabbits (Keyes and Compere,¹³ Tammann,¹⁴ Filippi¹⁵). The changes in the cartilage plates may be primary or secondary to degeneration of the disk or to disease within the bony vertebral body.

In discussing the normal histologic appearance of the plate it was pointed out that its central portion is often depressed and thinner than the remainder. We offered our opinion that this defect corresponded to the point of closure of the primitive notochordal canal. Either through persistence or through incomplete closure of the notochordal canal or secondary breakdown of the point of closure, nuclear material may be extruded into the spongiosa of the vertebral body, establishing the so-called *Knorpelknötchen* of Schmorl. Such defects as found in young subjects are readily recognized (fig 5). The intraspongious hernias are characteristically arranged one above the other through several segments. Histologically the gap in the cartilage plate is apparent and is usually fairly small, with little or no displacement of the margins as seen in traumatic rupture of the plate. The herniated material is obviously nuclear and often, especially in older specimens, shows at its periphery transformation into cartilage or pseudocartilage. The surrounding spongiosa tends to be thickened, walling off the hernia from the marrow spaces (fig 6). The subjoined disk is thinned but

¹³ Keyes, D, and Compere, E. The Normal and Pathological Physiology of the Nucleus Pulposus of the Intervertebral Discs, *J Bone & Joint Surg* **14** 897, 1932

¹⁴ Tammann, H. Ueber die Wundheilung im Bereich der Zwischenwirbelscheibe, *Arch f orthop u Unfall-Chir* **34** 356, 1934

¹⁵ Filippi, A. La guarigione del disco intervertebrale dopo asportazione del nucleus pulposus negli animali da esperimento, *Chir d org di movimento* [**20**] 1, 1935



Fig 5—Intraspinal hernia of nuclear material through small defect in the cartilage plate. The racemose-like form is characteristic of many of these hernias. There is little peripheral reaction.

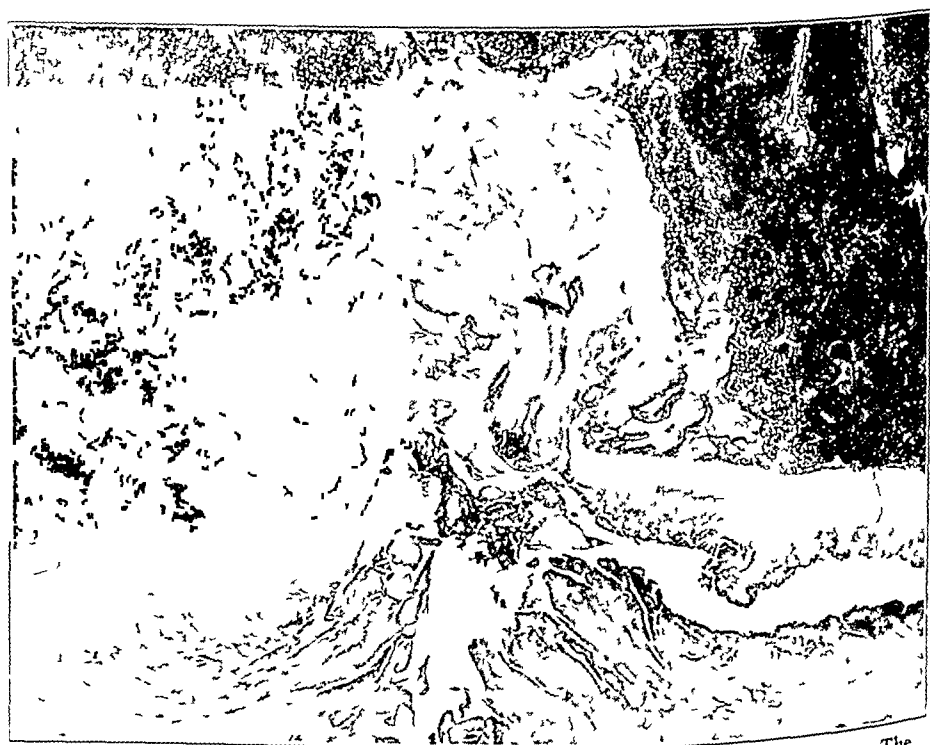


Fig 6—A typical nuclear prolapse with considerable bony encapsulation. The rent in the cartilage is clearly seen.

relatively intact at first, exhibiting little degeneration. Although we have not had the opportunity to examine many spinal columns of this type because of the difficulty of obtaining material from young subjects not suffering from a lethal condition, we are convinced from roentgen evidence that attendant degeneration of the disk sets in early and is often well established by the second decade. The significance of such herniations in the production of juvenile kyphosis will be discussed in a further section of the paper. However, changes which we take to be preliminary to the rupture of cartilage in youth may be



Fig 7—Protrusion of cartilage plate with small areas of fibrillation

seen in some specimens otherwise exhibiting a typical series of hernias. These changes occur at the summit of the aforementioned depressions in the cartilage plates and consist of a small area in which the cartilage cells are absent and replaced by fibrillated material (fig 7). We are uncertain as to whether to interpret these areas as scar formation or as evidence of the giving way of the cartilage plate at a point of weakness.

Not infrequently we have found a series of radiating fissures in the central part of the plate. These fissures are filled, on gross inspection, with a translucent material (fig 1A), which histologically appears to be a relatively structureless cicatrix. In the opinion of Bohmig⁸ and Uebermuth⁵ the fissures were formerly occupied by the vessels

which supplied the disk during development, which have undergone obliteration, and may be the starting point of the nuclear herniations of youth

Their great frequency in the cartilage plates of older specimens suggests, however, that they may, on the other hand, be of degenerative origin

Traumatic rupture of the cartilage plate occurs in conjunction with compression fracture of the vertebral body, but it has been remarked how often the disk escapes injury even in the most severe lesions. In these circumstances the nuclear material is widely dispersed in the spongiosa and after healing is partially absorbed and partly isolated by condensation of the surrounding spongiosa. The disk itself is markedly thinned and undergoes vascularization with fibrosis or even partial bony replacement in the later stages. An important variety of trauma to the cartilage plate is that associated with marginal fracture of the vertebral body. These chip fractures are commonly anterior in position and are in themselves insignificant but, from roentgen evidence, are followed by collapse and thinning of the disk. It would seem that the involvement of the disk is due to the extension of the fissure into the cartilage plate with attendant loss of nuclear substance and degeneration of the disk (Hanson,¹⁶ Janker,¹⁷ Joisten,¹⁸ Junghanns,¹⁹ Mikhailoff and Tcherepnin²⁰)

Rupture of the cartilage plate occurs secondary to loss of support by the spongiosa of the vertebral body. The commonest form is that associated with senile osteoporosis of the spine. The turgor of the nucleus balloons out almost the entire extent of the plates so that the disk acquires a highly biconvex form and the vertebral body intervening between two such disks becomes amphicelous. The most exaggerated examples are found in the lumbar region, where the disks are bulky. The cartilage plate exhibits fissures and breaks in continuity, and the herniation of nuclear material is usually massive, with little surrounding reaction. The remainder of the disk is relatively healthy.

16 Hanson, R. Some Anomalies, Deformities and Diseased Conditions of the Vertebrae During Their Different Stages of Development, Elucidated by Anatomical and Radiological Findings, *Acta chir Scandinav* 60 309, 1926

17 Janker, R. Die Epiphysen der Wirbelkörper und ihre Veränderungen "Persistierende Wirbelkörper-epiphysen," *Fortschr a d Geb d Röntgenstrahlen* 41 597, 1930

18 Joisten, C. Ueber persistierende Apophysen an der Lendenwirbelsäule, *Arch f Orthop* 28 622, 1930

19 Junghanns, H. Gibt es "persistierende Wirbelkörper-epiphysen"? *Fortschr a d Geb d Röntgenstrahlen* 42 704, 1930

20 Mikhailoff, M., and Tcherepnin, M. I. Ueber die Wirbelkörperinseln und deren Röntgenbild, *Fortschr a d Geb d Röntgenstrahlen* 40 1061, 1929

Similar rupture of the cartilage plate follows loss of bony support due to invasion of the vertebral body by infection or tumor (fig 8)

The cartilage plate does not escape in the general process of degeneration of the disk found with advancing age. In senile osteoporosis as discussed in a foregoing paragraph, the rest of the disk is fairly normal in character, and, in addition, the rupture is usually single. The degree of involvement of the cartilage plate in degeneration of the disk varies considerably. In some specimens the changes elsewhere may be advanced and the cartilage plates relatively intact. In others the changes in the plate are extensive. It is not uncommon to find, on gross examination, multiple large jagged fissures (fig 9). Histologically, numerous patches are found where the cartilage matrix is frayed and replaced by a poor fibrous scar, which may extend partially or entirely through the thickness of the plate. Erosion in multiple areas by the ingrowth of granulation tissue from the marrow spaces is common and when extensive is accompanied by marked vascularization and fibrosis of the disk. The original plate may be represented by small islands of cartilage only, a compact scar or area of ossification replacing it. Under these circumstances the herniations of nuclear material into the spongiosa are small, irregular and not so centrally localized as in other forms. As to the interpretation of these changes, it is difficult if not impossible to say whether the damage to the cartilage plate is the result of the numerous small traumas of daily life acting on developmentally faulty cartilage plates with secondary degeneration of the disk, as contended by some, or whether the cartilage simply participates in the general senile decay of the disk.

The nucleus pulposus varies considerably in structure from infancy to old age. In infancy the nucleus is well defined, and its line of demarcation from the annulus is distinctive. Histologically it consists of a fairly loose network of cells of primitive mesenchymal type and physaliferous cells of Virchow. By the second decade the transition from nucleus to annulus is much less definite. The cells are fewer, and the delicate fibrous processes, as described under normal histologic aspects, are more apparent. In the middle decades, normally the fibrous elements are still more definite, and the disk is more homogeneous. At this stage cavities in the central zone are frequent, and villous processes are in evidence. These cavities contain a gelatinous fluid and, on microscopic examination, some cell debris. Nests of cartilage cells are found scattered throughout the nucleus, and in the subchondral region there is some transformation into organized fibrocartilage. Thereafter the disk undergoes progressive dehydration and fibrosis.

It should be borne in mind that there is a progressive change in nuclear architecture from decade to decade. Pathologic conditions must be interpreted in the light of such progressive changes.

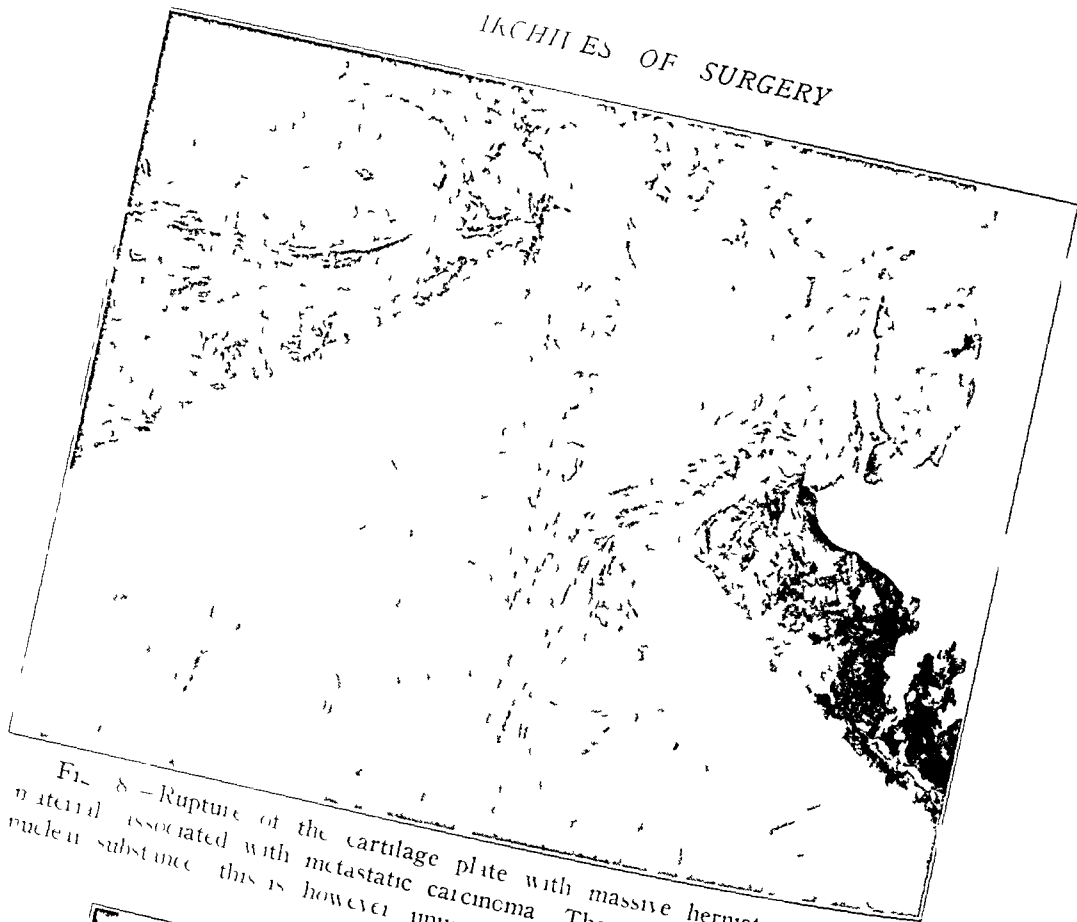


Fig. 8—Rupture of the cartilage plate with massive herniation of nuclear material associated with metastatic carcinoma. There is slight invasion of the nuclear substance; this is however unusual.

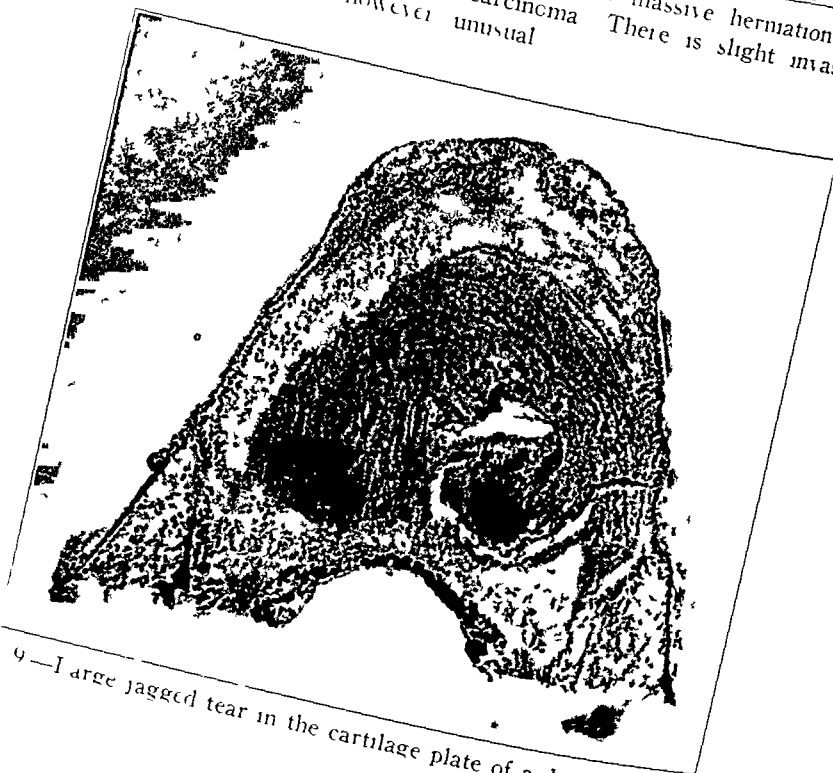


Fig. 9—Large jagged tear in the cartilage plate of a degenerated disk.



Fig 10—Exaggeration of the nucleus and nuclear cavitation as seen in a lumbar disk

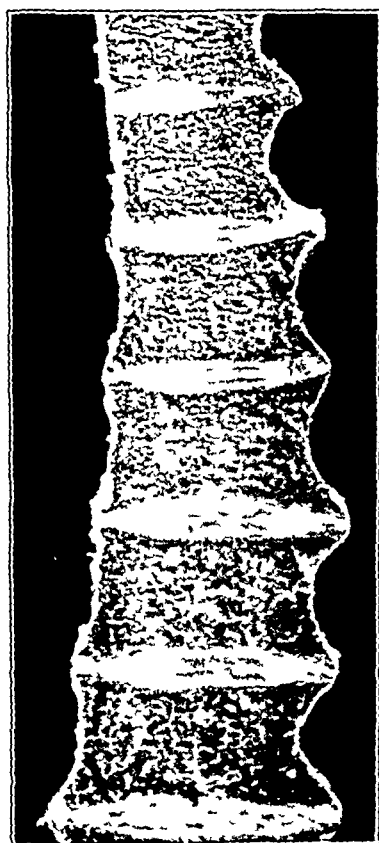


Fig 11—Coronal section of the thoracolumbar portion of the spinal column. Note the parallel areas of "brown degeneration" in the subchondral zone and collapse of the disks

Degeneration may occur as early as the third decade or before if the integrity of the disk has been interfered with by trauma or congenital defects in the restraining cartilage plates. Grossly the earliest change would seem to be an exaggeration in the size of the nucleus and an excessive extent and development of nuclear cavitation (fig 10). Such disks appear to be deficient in turgor and elasticity. Further development would seem to be in the breakdown of the fibrillary structure and the dissolution of the cellular elements, until the whole nucleus is reduced to an amorphous mushy mass which consists of cell debris-necrosis. In this mass quite rarely calcium salts are deposited.

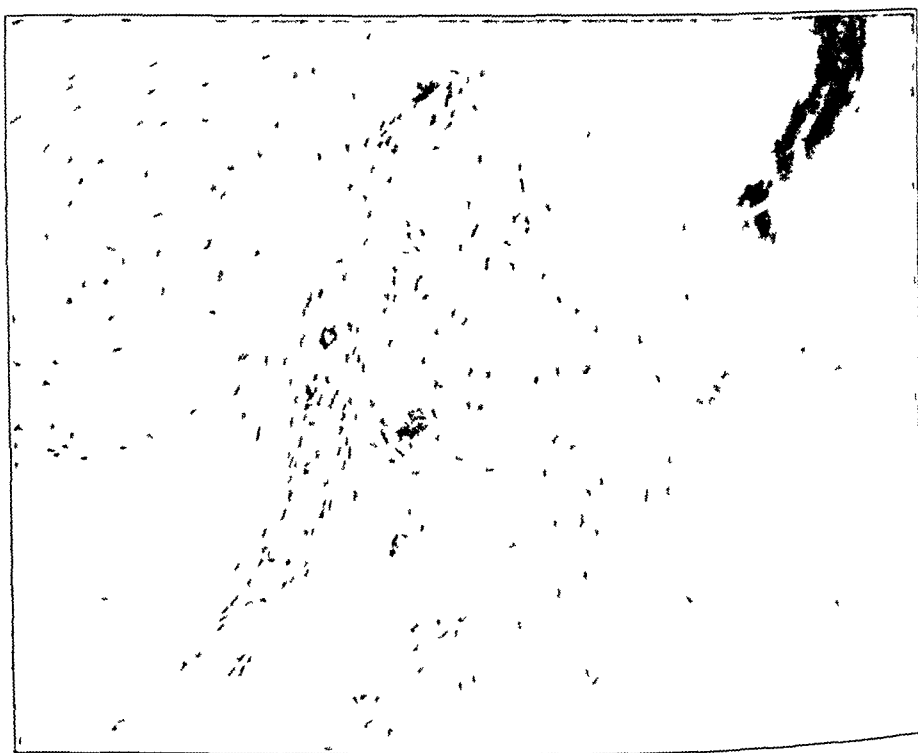


Fig 12—Microscopic view of the annulus showing commencing vascularization and fibrosis

By this time minor defects and erosions of the confining cartilage plates have appeared, which may rupture and lead to the escape of nuclear material. On the other hand, areas of so-called "brown degeneration" appear beneath the cartilage plates (fig 11) and seem to be the result of hemorrhage from fine vascular tufts which have invaded the disk through the cartilage plates. From loss of turgor, the disk has usually by this time undergone almost complete collapse.

Various stages of repair may ensue, consisting initially of an increase of fibrous and cartilaginous elements, tending to replace the nuclear

material. This may proceed to a point where the disk by further vascularization is partially or completely replaced by bone (fig 4)

Extruded nuclear material shows a marked tendency to become transformed at its periphery into cartilage or pseudocartilage, and the

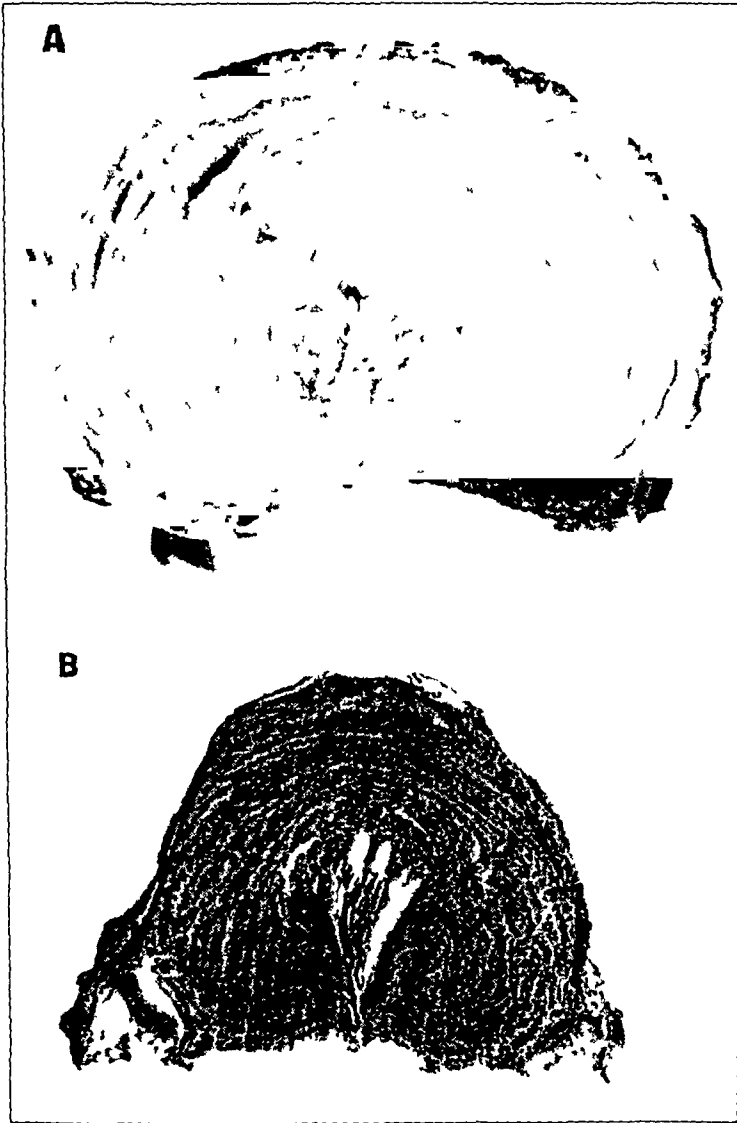


Fig 13—*A*, disk showing anterior crescentic fissures in the annulus. *B*, dorsal radial fissure with slight escape of nuclear material.

process may go on to ossification. More central portions tend to show an increase in the number of cartilage cells or to become transformed into fibrous tissue when there is evidence of vascularization.

The annulus fibrosus likewise shows progressive changes during its life history. With increasing age the fibrous lamellae become more

and more definite and larger. With the onset of degeneration the inner layers merge into the expanding nucleus until little more than a ring of the original tissue persists (fig 10). During this process the lamellae become more swollen, some areas show necrosis, and vascularization commences (fig 12). The fibrous bundles may separate, producing concentric fissures, some of which may extend through the entire thickness in a radial direction. The concentric fissures are most frequent anteriorly (fig 13A) and occur most characteristically in kyphosis of old age.



Fig 14—"Brown degeneration" extending in crescentic fashion between the bundles of the annulus.

The radial fissures are most often found dorsally (fig 13B), and through them nuclear material may herniate into the vertebral canal. Necrosis is far less common in the annulus than in the nucleus and is more often found anteriorly. In conjunction with necrosis, small areas of calcification are found, and these may lead to formation of isolated bony deposits if these areas are adequately vascularized. As in the nucleus, areas of so-called "brown degeneration" may be found, and these areas tend to lie crescentically between the bundles of the annulus (fig 14). In our opinion they are the result of hemorrhage from delicate vascular channels. With the collapse of the disk, the annulus as a whole tends to be displaced peripherally and bulges in all directions.

The annulus may show evidence of attempts at repair. Initially, notably in the lumbar region, it may take on an exaggerated fibrocartilaginous appearance. With the increasing vascularization, the fibrous cellular elements are greatly increased. The change at the peripheral zone of junction with the vertebral body is a special feature. Here, hyperplasia of the fibrocartilage tends to increase the thickness

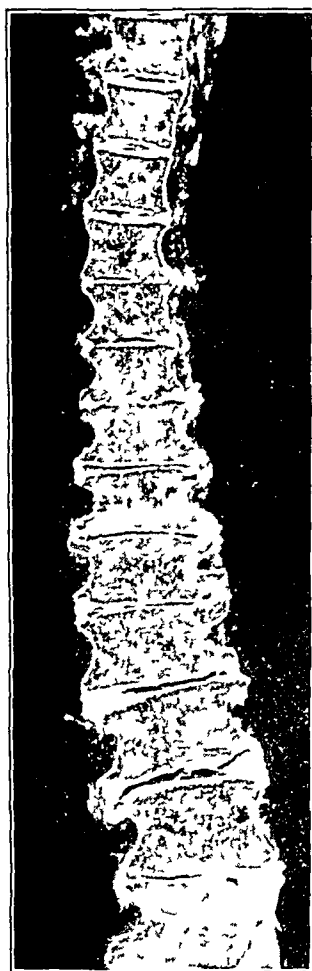


Fig. 15—Coronal section of the thoracolumbar portion of the spinal column, showing marked dissolution and collapse of the intervertebral disks, lateral displacement of the vertebrae and osteophyte formation.

of the annulus and its vascularization is attended by the formation of osteophytes. We feel that the formation of osteophytes does not occur in the original annulus material but in the superadded tissue which is developed as a repair mechanism in response to the increasing strain thrown on the peripheral junction by the progressive collapse of the disk and the development of shearing forces set up in the lateral dis-

placements of the vertebral segments as in the scoliosis of arthritis deformans (fig 15)

Posterior Displacements—Dorsal protrusions, displacements or herniations of disk tissue merit separate consideration because of their special significance in causing pressure on the contents of the neural canal



Fig 16—Sagittal section of the cervical portion of the spine, showing fairly large protrusion and herniation of the fourth, fifth and sixth cervical disks. There is some indentation of the spinal medulla.

Extradural tumors, variously termed chondromas, fibromas, fibrochondromas, chondrochordomas, exostoses and ecchondroses, have long been described as occurring most frequently in the lumbar and cervical regions. These so-called tumors are now clearly recognized as being due to displacement of disk tissue dorsally.

From the pathologic point of view, posterior displacements of the disk tissue are formed with the greatest frequency in the spinal columns of elderly persons. Andrae²¹ reported finding cartilaginous nodules on the dorsal aspects of 15 per cent of 368 columns examined. They are found most frequently in the lower thoracic and lumbar regions and are nearly always attended by definite evidence of disk degeneration. The thoracic protrusions tend to be small and insignificant, often buried beneath the posterior longitudinal ligament. In the lumbar and cervical regions they are larger and frequently extend to one or other side of the midline (fig 16).

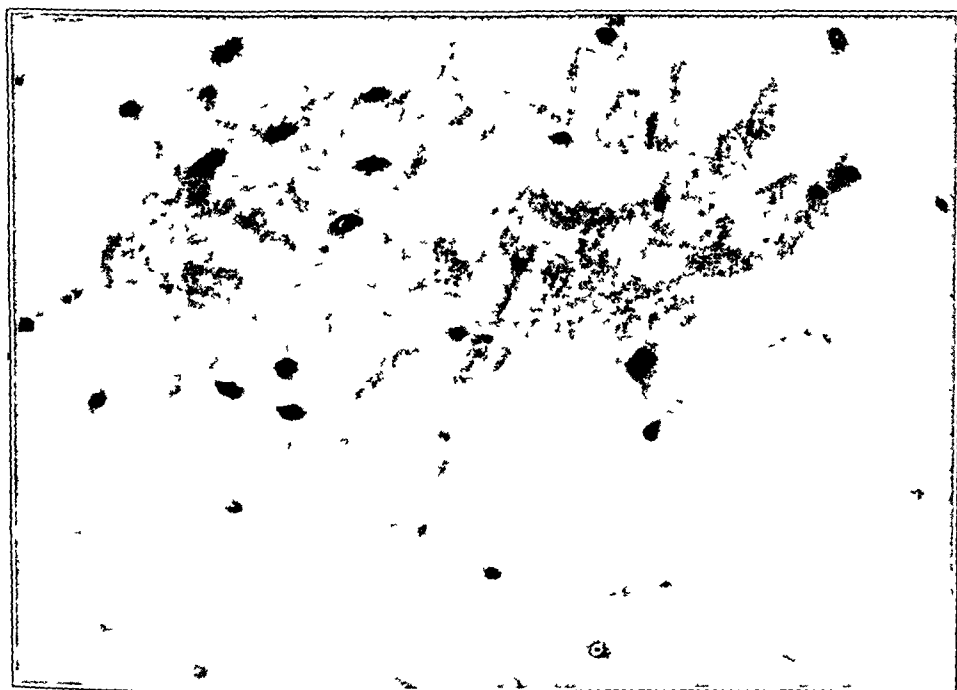


Fig 17—Characteristic nuclear material removed operatively from a dorsal herniation

Histologically the material obtained post mortem or at operation presents an extremely variable picture. In some specimens the structure is characteristically that of the nucleus pulposus, although as a rule the cellular elements are increased and there is true inflammatory reaction (fig 17). In others, and perhaps the great majority, there is a mixture of pulposal and annular material showing a varying degree of cartilaginous metaplasia, inflammatory reaction or necrosis. We have observed in a specimen a portion of the confining cartilage plate

²¹Andrae, R. Ueber Knorpelknoten am hinteren Ende der Wirbelbandscheiben im Bereich des Spinalkanal, Beitr z path Anat u z allg Path 82 464, 1929

in the protruded tissue. Those of long standing, and therefore obtained on postmortem examination, show a great abundance of cartilaginous transformation with areas of calcification and after-vascularization, even of bone.

Some discussion has arisen as to whether these nodules are herniations of nuclei pulposi or protrusions of intervertebral disks. In our opinion both varieties may be found. In some cases we have seen fissuring of the annulus surrounded by "brown degeneration" with herniation of nuclear material. In others we have found collapse of the disk and protrusion of the annulus with or without herniation of the nucleus. These findings are nearly always attended by profound disk degeneration. In regard to younger subjects with otherwise healthy disks the question arises as to whether trauma is not the main causal agent. We doubt that in such subjects trauma would rupture the annulus, it would be more likely to fissure the cartilage plate at the junction with the annulus, and the finding of a portion of the plate in the extruded material is suggestive of this mechanism.

We should like to emphasize that posterior herniations are in the great majority of instances evidence of general disk degeneration.

PATHOLOGIC OBSERVATIONS IN SPECIAL CONDITIONS

Infections and Tumors—The disks seldom appear to be involved either primarily or secondarily in disease processes, whether these are infectious or malignant. The cartilage plates, like the epiphysal plates of long bones, are apparently extraordinarily resistant to invasion. In the more acute destructive processes, e. g., staphylococcic osteomyelitis, the disk may undergo necrosis and be completely destroyed. In the less destructive, there may be erosion of the cartilage plate with ingrowth of granulation tissue and scarring of the disk. It is said that in other forms of spondylitis, as in typhoid spine, the disks escape.

Tuberculosis is notable in that the disk is nearly always involved secondarily. We have noted multiple erosions of the cartilage plate by granulation tissue in the early stages and minute ruptures with escape of nuclear material into the spongiosa. Eventually the disk is partially destroyed and is replaced by bone in healing or is displaced during the stage of collapse.

The disks may be involved in syphilitic spondylitis and in the late stages of syphilitic osteoarthropathy as well as in syringomyelia.

The disks are even more resistant to invasion by tumors. In the presence of tumors with associated osteolysis the disks tend to bulge into the spongiosa but not nearly to the same extent as in senile osteoporosis. Loss of support to the cartilage plates frequently leads to their rupture, with massive herniation of nuclear material into the spongiosa (fig 8).

Primary tumors of the disk or of its derivatives, the chondromas, are rare and scarcely warrant discussion here

Adolescent Kyphosis—Clinically, adolescent kyphosis is a well defined condition, displaying typically the following characteristics. It is reported to occur in males more frequently than in females, although in our opinion this difference in incidence is more apparent than real. The deformity is essentially a rigid rounded kyphos, centered usually between the seventh and tenth thoracic vertebrae, and in less than half the cases there are associated unimportant lateral curves. The kyphos is rarely discernible before the age of 10, the onset is most frequent between the ages of 15 and 17 years. The patients are nearly always rapidly growing healthy persons with excellent musculature. Pain is an inconstant complaint and is usually in the nature of an ache on exertion.

The roentgen appearance of the involved vertebrae is distinctive. The changes are first seen in the subchondral bone adjacent to the intervertebral disk and are better observed in lateral than in anteroposterior projections.

The first deviation from the normal appearance is an irregularity of the subchondral bone at the superior and inferior surfaces of the vertebral bodies. These surfaces, instead of appearing as a thin smooth continuous distinct line in the roentgenograms, become irregular and broken. The intervertebral disk is always narrowed. In the vast majority of cases sizable herniations of the nuclear material into the spongiosa are indicated by sclerosis of the adjacent bones. These herniations vary in size, number and position. In older lesions the abnormal transmission of weight from vertebra to vertebra in the region of the kyphos leads to wedging of the vertebral bodies, sclerosis of the anterior portions of the superior and inferior surfaces of the vertebrae and osteophyte formation. We have noted that in the cases of adolescent kyphosis which show early the most marked changes in the subchondral bone there is often associated a definite platyspondylia of the involved vertebra.

The cause of this condition is still obscure. Several hypotheses have been advanced by various authors. Schanz²² and his pupil Elsner²³ expressed the opinion that the condition was related to the effects of heavy work on a growing spine. Eichelbaum²⁴ suggested

22 Schanz, A. Eine typische Erkrankung der Wirbelsäule (Insufficiencia Vertebrae), Berl klin Wchnschr 44 986, 1907

23 Elsner, J. Ueber Lehrlingsskoliose, Ztschr f orthop Chir 32 277, 1913

24 Eichelbaum, K. Ergänzende Bemerkung zur Arbeit Schildbach "Die Entwicklung der juvenilen Kyphose" Zentralbl f Chir 64 2894, 1937

muscular insufficiency as the primary cause. Scheuermann²⁵ regarded the disease as an epiphysitis and termed it osteochondritis deformans juvenilis dorsii. Schmorl²⁶ advanced the strongest evidence to show that the kyphosis is the direct result of alterations in the intervertebral disks, a view which has received considerable support (Calvé,²⁷ Beadle¹⁰). He demonstrated by postmortem evidence that prolapse of the nucleus pulposus into the spongiosa of the vertebral bodies may occur, even in children, as the result of congenital weakness or defect of the cartilage plates. The histologic appearance of these protrusions has already been discussed under general pathologic observations. Disturbances of the cushioning effect of the nucleus in overloading and trauma lead to secondary changes in the epiphyses and bodies of the vertebrae. Roentgenologically the presence of such hernias cannot always be discovered, which is explained as being due to the absence of reactive changes in the bone for it is not the prolapse but the sclerosis of bone about the prolapse which renders Schmorl's *Knorpelnotchen* visible. It is true that in many cases these notches become evident only in the later stages of the disease. Schmorl's theory has not been without criticism even by its supporters.

Schmorl,²⁸ in criticizing Scheuermann's conception that the condition is epiphysitis, put forward the extraordinary view that the epiphysis of the vertebra is in no way analogous to the growth epiphysis seen elsewhere and that it has nothing to do with growth processes. He would regard the epiphysis as in the nature of a mechanism giving eventual bony fixation to the annulus. We find this view totally unnecessary to Schmorl's thesis, and it is certainly not borne out by the experimental

25 Scheuermann, H. Kyphosis dorsalis juvenilis, *Ztschr f orthop Chir* **41** 305, 1921, Cyphose juvenile, *Arch med belges* **81** 353, 1928, Zur Roentgen symptomatologie der juvenilen Osteochondritis dorsii, *Fortschr a d Geb d Rontgenstrahlen* **44** 233, 1931, Roentgenologic Studies of the Origin and Development of Juvenile Kyphosis, Together with Some Investigations Concerning the Vertebral Epiphyses in Man and in Animals, *Acta orthop Scandinav* **5** 161, 1934.

26 Schmorl, G. Die Pathogenese der juvenilen Kyphose, *Fortschr a d Geb d Rontgenstrahlen* **41** 359, 1930, Bemerkungen zu der Arbeit von Mau zur Frage der Pathogenese beziehungsweise der pathologischen Anatomie der Adoleszentenkyphose, *Ztschr f orthop Chir* **55** 274, 1931, Ueber die pathologische Anatomie der Wirbelbandscheiben, *Beitr z klin Chir* **151** 360, 1931.

27 Calvé, J. Osteo-chondrite vertebrale infantile, *Bull Soc pediat de Paris* **25** 489, 1927, Osteo-chondrite vertebrale infantile, in *The Robert Jones Birthday Volume. A Collection of Surgical Essays*, London, Oxford University Press, 1928, p 315.

28 Schmorl, G. Zur Kenntnis der Wirbelkorperepiphyse und der an ihr vorkommenden Verletzungen, *Arch f klin Chir* **153** 35, 1928, Zur Sektions technik der Wirbelsäule, *Zentralbl f allg Path u path Anat* **47** 7, 1930. Schmorl and Junghanns ¹²

work of Haas²⁹ or by clinical observation, as is seen in fusion of the spine in children. Growth from this epiphysis is very slow and is extended over many years, which accounts for its histologic appearances, which lack the usual columnar formation.

Senile Kyphosis—Senile kyphosis has been recognized for many years and grouped in a somewhat confused manner with the deforming conditions of old age. Schmorl,³⁰ recognizing the primary changes as a special type of destruction of the disk, segregated senile kyphosis as a distinct entity. The characteristic feature of this condition is the spinal curvature, which appears usually late in life and develops rapidly as an exaggeration of the physiologic thoracic curve. The curvature is most marked in the upper thoracic part of the spine and may progress to a high degree.

Roentgenologic and pathologic studies of senile kyphosis reveal the following progression of events. With commencing kyphosis there is narrowing of the intervertebral disk anteriorly together with increasing sclerosis of the anterior borders of the vertebral bodies. There may be some degree of osteophyte formation, but usually it is not marked. The anterior compression of the disk continues until the vertebral bodies contact each other at their anterior borders. The intervening disk tissue is destroyed and replaced by bone, and thus the involved vertebral bodies are fused anteriorly with a continuous bridge of bone. The posterior portions of the intervertebral disks usually show a fair degree of preservation (fig. 4).

Postmortem studies on senile kyphosis indicate that the essential pathologic process is pressure necrosis of the anterior portion of the intervertebral disk. The abnormal pressure on the anterior portion of the disk, leading to its necrosis, results from general loss of muscular tone in the aged and the failure of the senile inelastic disk to disperse adequately the compression forces applied to it. The vertebral bodies do not become wedge shaped to any great degree in senile kyphosis inasmuch as the anterior narrowing of the disk is sufficient to account for the deformity.

Spondylosis Deformans—The conception that spondylosis deformans is the outcome of degeneration of the intervertebral disks is now generally accepted by most investigators in this field. The fundamental lesion is the change in the intervertebral disk leading to its progressive deterioration and functional failure. The pathologic

29 Haas, S. L. Growth in Length of the Vertebrae, Arch Surg **38** 245 (Feb.) 1939.

30 Schmorl, G. Zur pathologischen Anatomie der Wirbelsäule, Klin Wchnschr **8** 1243, 1929, Ueber die pathologische Anatomie der Wirbelbandscheiben, Beitr z klin Chir **151** 360, 1931, Beiträge zur pathologischen Anatomie der Wirbelbandscheiben und ihre Beziehungen zu den Wirbelkörpern, Arch f orthop u Unfall-Chir **29** 389 1931. Schmorl and Junghanns.²²

processes seen in the spinal column as dependent on degeneration of the disks may not necessarily be related to the age of the patient. Spondylosis deformans may appear as early as the third decade of life. It affects every one if sufficient time elapses. The frequency naturally increases with age and approaches 100 per cent at the age of 90 years (Schmoil and Junghanns¹²). The disks, through age or individual predisposition, lose elasticity and, under the influence of continuous functional trauma, pass through the various stages of degeneration: fibrillary degeneration, brown degeneration, cartilage plate rupture, nuclear prolapse, necrosis, fissuring, hemorrhage, vascularization and reactive changes.

In spondylosis deformans disk degeneration is usually generalized throughout the spinal column (fig 15). There is dissolution with loss of substance in the nucleus pulposus, followed by relaxation and protrusion of the annulus about the periphery. This leads to lateral shifting of the vertebral bodies. The loss of turgor of the nucleus permits increased mobility between the segments with strain on the ligamentous structures and formation of osteophytes. Osteophytes tend to occur adjacent to the spinal ligaments and appear earliest in those areas of the spinal column that are subjected to the greatest movements. Nonappearance of osteophytes posteriorly may be accounted for by the fact that movement between the vertebral bodies is less posteriorly than anteriorly.

Ankylosing Spondylitis—Ankylosing spondylitis is considered by the more recent observers as rheumatoid arthritis involving primarily the small articulations of the spinal column. There follows smooth ossification of the anterior longitudinal ligament and of the outer layers of the annulus without formation of osteophytes. The disks disappear to a greater or lesser extent and are replaced by bone.

Investigations in our clinic (Rinehart and associates³¹) indicate a relationship of vitamin C to all forms of rheumatoid arthritis and particularly to ankylosing spondylitis.

Mr Leonard Taix and Mr Robert Ray made the photographs

31 Rinehart, J. F., Greenberg, L. D., Baker, F., Mettier, S. R., Bruckman, F., and Choy, F. Metabolism of Vitamin C in Rheumatoid Arthritis. *Arch. Int. Med.* 61: 537 (April) 1938.

COMPRESSION OF SPINAL CORD AND NERVE ROOTS BY HERNIATION OF THE NUCLEUS PULPOSUS IN THE CERVICAL REGION

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NEW YORK

In 1927 there was brought together for the first time, as representing a clinical entity, a group of unusual "tumors" arising from the cervical intervertebral disks (Stookey). Scattered reports of such lesions had appeared previously, notably Adson's report of a case and a mention of one by Elsberg in his "Tumors of the Spinal Cord." The condition, however, was not generally recognized as distinct from other vertebral tumors and no reference to it is to be found in such standard texts as those of Elsberg, Bruns, Schlesinger, Lubarsch and Osterlag and Antoni.

On the basis of the histologic picture and because at the time no other explanation of the tumor-like masses seemed plausible, they were regarded as chondromatous new growths and were designated ventral extradural cervical chondromas. The extensive studies of Schmorl (1929) and Andrae (1929) on the spinal column and their elucidation of the nature and structure of the nucleus pulposus have since led to a revision of this view and it now seems evident that the lesions are not neoplastic but represent rather herniation or protrusion of the nucleus pulposus through the annulus fibrosus, sometimes with secondary changes, such as calcification. True chondromas may indeed be found but are certainly far less common than herniated disks.

Following the publication of my original paper, numerous reports of protrusion of intervertebral disks appeared, including those of Dandy, Bucy, Alajouanine and Petit-Dutailis, von Pechy, Elsberg, Antoni, Mixter and Barr, May, Alpers, Grant and Yaskin and others. Mixter and Ayer reported a series of 34 cases of vertebral herniation, in 8 of which the protrusion was in the cervical region. Hawk in 1936 collected from the literature 16 cases of protrusion of cervical disks and reported 1 new example.

The ventral extradural cervical herniated disk is a discrete, sharply circumscribed mass, seldom exceeding 1.5 cm. by 1 cm., consisting of thin layers of frayed cartilaginous tissue, which are readily separated. It lies in front of the dural sac, in or to one side of the midline. Unlike the large paravertebral new growth, which invades the spine secondarily,

the herniated mass arises within the vertebral canal. It is found for the most part in relation to the freely movable vertebrae of the mid cervical region, an area especially liable to repeated minor strain and stress but seldom the site of sudden severe trauma, such as occurs in the lumbar region as a result of heavy lifting or of a fall on the buttocks.

A history of sudden onset associated with injury is thus rarely obtained in herniations of the cervical region. It seems likely that the cervical protrusion is primarily a degenerative lesion associated with repeated traumas of minor degree. As a result of such traumas or in the course of the degenerative process, a slight fissure occurs in the posterior portion of the annulus, through which the nuclear mass protrudes. Judging from the clinical histories, the protrusions in the cervical region occur gradually and are seldom sudden or violent. In

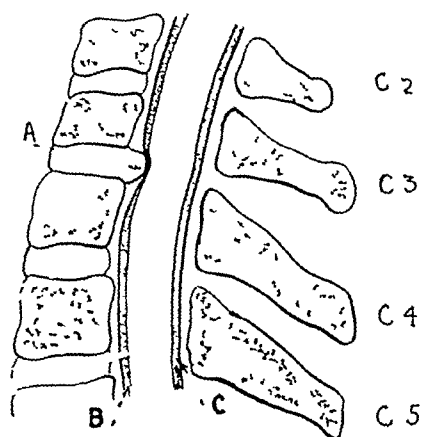


Fig. 1—Schematic drawing showing extradural ventral protrusion of the nucleus pulposus. *A* indicates protrusion of the nucleus pulposus, *B*, spinal fluid buffer, *C*, dura. (From Stookey, 1928.)

the latter case, since protrusions in this region impinge, as a rule, on the spinal cord and not on the nerve roots, as in the lumbar region, signs referable to the cord would at once be evident, for sudden trauma to the spinal cord is far more likely to give rise to obvious clinical signs than similar trauma to nerve roots. The onset of symptoms of a cervical protrusion, however, is usually gradual and slowly progressive.

INCIDENCE

Both Schmorl and Andrae noted that while protrusion in the lumbar region is of frequent occurrence, protrusion in the cervical region is rare. This is borne out by a study of the literature. Since the recognition of cervical protrusion as a definite clinical entity, in 1928, relatively few examples have been recorded, whereas the study of cases of herniation in the lumbar region by Mixter and Barr was followed by a

large number of reports, notably those of Adson and Craig and Love, from the extensive material of the Mayo Clinic, Spurling, and Semmes.

The majority of cervical disk herniations occur in men of late middle age. The youngest of my patients was 44 and the oldest 68 years old, the average age was 53 years. In Elsberg's later series, which included many tumors of the lumbar and thoracic region as well, the ages ranged from 38 to 68 years, with an average of 50.

SIGNS AND SYMPTOMS

The symptoms of herniation of a vertebral disk are due to pressure of the cartilaginous mass on the cord and nerve roots. They vary with the size and position of the protruded portion.

Syndrome of Bilateral Ventral Pressure—When the mass is so situated as to exert bilateral pressure, displacing the cord as a whole, the picture is that of any ventral neoplasm of the spinal cord. The presenting symptoms of such herniations show no constancy, in spite of the apparently close resemblance of the protruded masses in size, shape and position. So compact is the arrangement of the fiber tracts carrying the various impulses in the spinal cord that the slightest variations in the position of a discrete mass are reflected in the clinical picture. Among the initial symptoms which have been observed in this group are pain and a sensation of intense cold, with numbness, spasticity and weakness, in both lower extremities and gradual weakness and hypotonia in the muscles of the upper extremity, together with atrophy and fibrillation, though the latter may be absent.

The sensory disturbances are bilateral, involving pain and temperature sensation, with blunting of tactile discrimination as well as of crude tactile sensation. Vibratory sensation may also be impaired, although muscle, joint and tendon sense may or may not be affected. This dissociation of vibratory and muscle, joint and tendon sense has frequently been observed in the presence of tumors of the spinal cord and after their removal, when restoration of vibratory sensation is delayed some time after the return of all other forms of sensation. It has been suggested, in an attempt to explain this dissociation, that these impulses may be carried not only in the posterior column but in a separate pathway outside the latter. A more likely explanation would seem to be that there exists a difference in resistance to the transmission of the impulses along the fibers of the dorsal column, conduction of vibratory sensation being more easily impaired than that of muscle, joint and tendon sense. Varying degrees of pressure exerted on a nerve in a muscle-nerve preparation have been shown experimentally to interfere selectively with the conduction of impulses. A similar mechanism probably holds for fibers within the spinal cord.

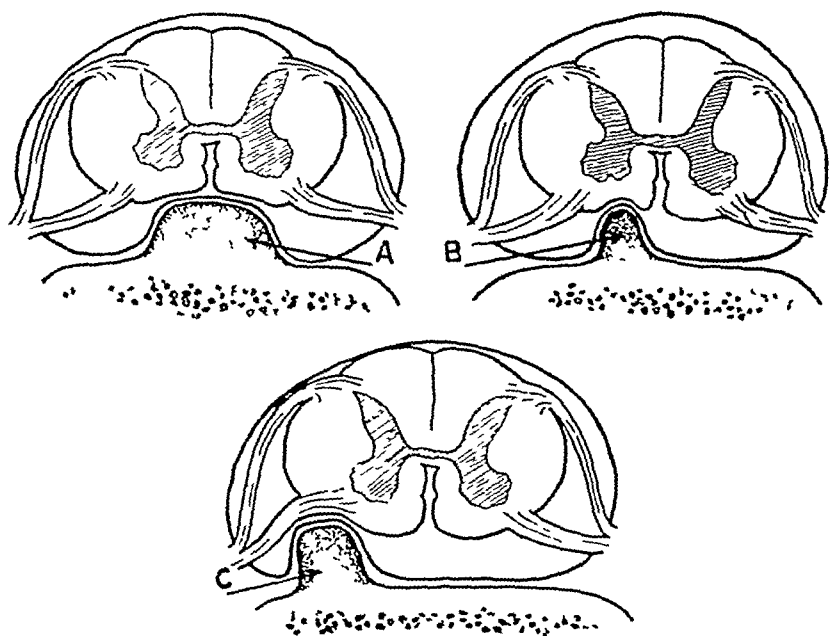


Fig 2—Schematic drawing to show variations in the position of the protrusion. *A* produces the syndrome of bilateral ventral pressure, *B*, the syndrome of unilateral pressure, *C*, the syndrome of root pressure. (From Stookey, 1928)

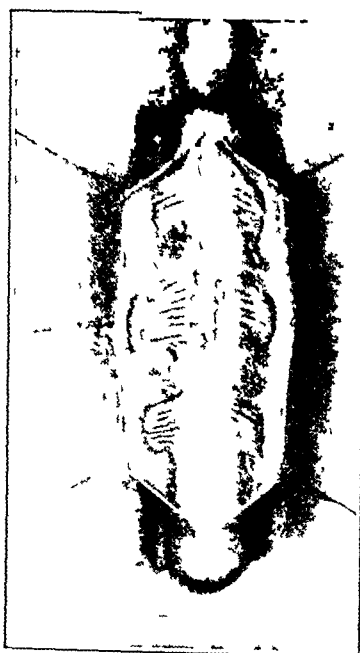


Fig 3—Bilateral exposure of the cervical cord showing slight dorsal angulation of the cord caused by extradural ventral herniation of the nucleus pulposus. (From Stookey, 1928)

The signs in this group are essentially those of any ventral mass of sufficient size to exert bilateral pressure on the spinal cord with a maximum of pressure on the ventrolateral columns. They present no essential problem in diagnosis. They should readily suggest a ventrolateral tumor of the spinal cord and lead to appropriate measures.

If, however, the protrusion is narrow and situated in the midline, pressure may be exerted only on the ventral gray column and on both emerging ventral roots, without impingement on the more laterally placed spinothalamic tracts or the more dorsal pyramidal tracts. In this event

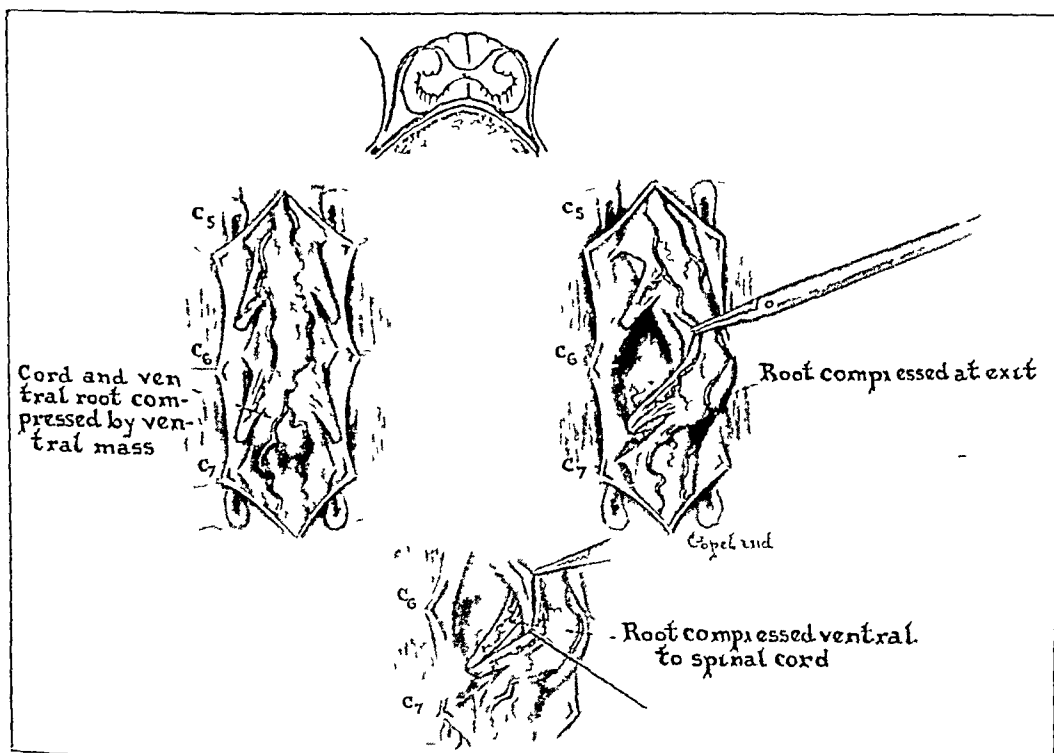


Fig 4—Small protrusion exerting bilateral pressure on both anterior horns and both ventral roots but not compressing the pyramidal or spinothalamic tracts

the signs are referable to the ventral gray columns alone—atrophy, hypotonia and fibrillary twitchings limited to the muscles supplied by a single segment. Recently I operated on a patient with these findings, due to this type of protruded disk. No sensory changes were observed, and no signs of disturbance of the long fiber tracts were elicited. A definite ventral protrusion compressing both ventral gray columns and both ventral roots at their emergence was encountered.

Syndrome of Unilateral Ventral Pressure—In this group of cases the herniated portion is small and is so placed that it exerts unilateral

pressure on the ventral columns of the cord, producing signs of involvement of the unilateral pyramidal tract in the lower extremity on the side of the protrusion, with local weakness and atrophy on the same side in the muscles of the cervical segments at the level of the compression. Changes in pain and temperature sense occur on the opposite side of the body at a level several segments lower than the focal motor signs.

Thus the syndrome consists of focal atrophy of the lower motor neuron type at the level of the lesion, spasticity and pyramidal tract

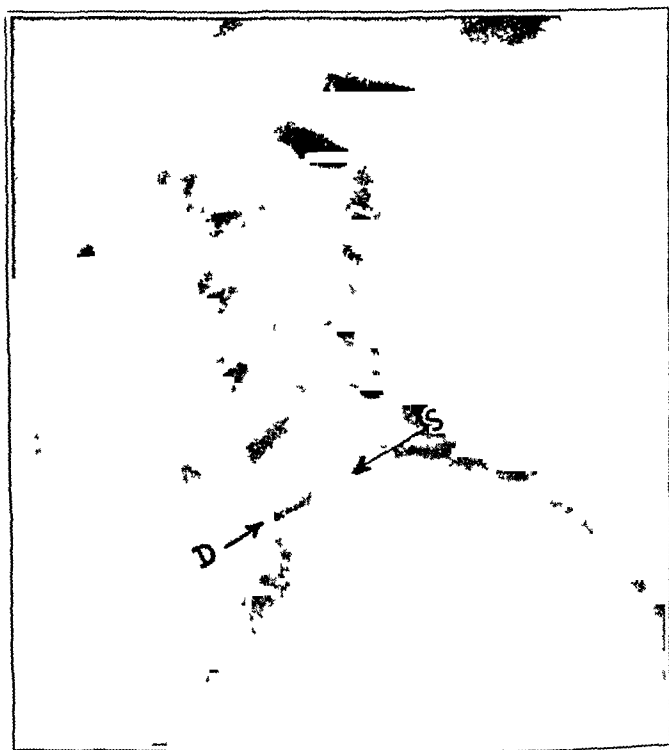


Fig 5—Roentgenogram of the cervical portion of the spinal column of the patient whose lesion is shown in figure 4. Note the narrow intervertebral disk between the bodies of the sixth and seventh cervical vertebrae (*D*) and spurs (*S*) projecting into the intervertebral foramen.

signs of the upper motor neuron type below the level of the lesion on the same side, and dissociated sensory changes on the opposite side.

The presenting symptom in these cases may be pain or stiffness of the neck, associated with pain or weakness in the region of the shoulder girdle, arm, forearm or hand, depending on the segment involved.

The *motor signs*, produced by pressure on the ventral gray matter, consist, as suggested, in rather sharply localized atrophy and fibrillations involving the muscles on the same side and indicating quite clearly the

level of cord compression. Thus, with pressure at the level of the fifth and sixth cervical segments, the deltoid, biceps, supraspinatus and supinator longus muscles are affected, whereas, pressure at the level of the eighth cervical segment will produce fibrillation and atrophy of the intrinsic muscles of the hand.

The *sensory disturbances*—loss of pain and temperature sense on the opposite side—are due to pressure on the spinothalamic tract. While

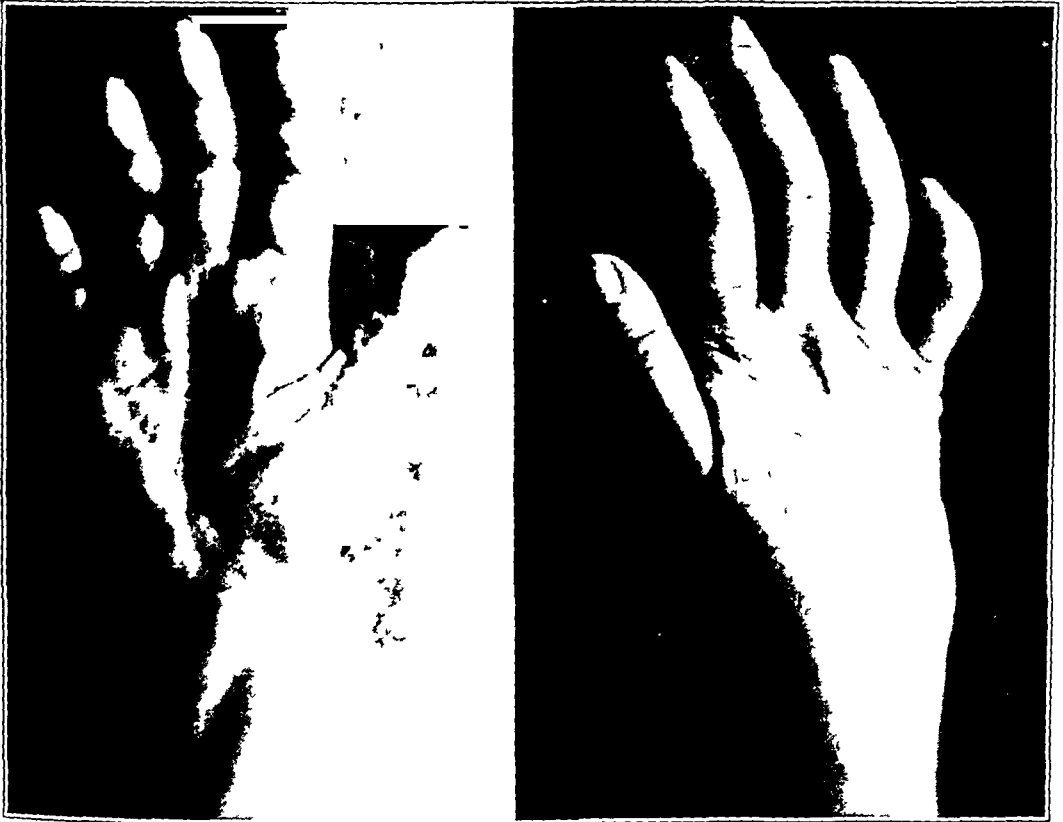


Fig. 6—Hands of the patient whose lesion is shown in figure 4. Note the atrophy of the intrinsic muscles of the hand and *main en griffe* due to compression of the ventral horn and ventral roots by herniation of the nucleus pulposus.

the sensory changes are definite, they are likely to be misleading as an indication of the site of compression, since the sensory level is several segments lower than the motor level. This is to be explained by the fact that the incoming pain and temperature fibers cross obliquely in the spinal cord and do not reach the contralateral spinothalamic tract for a distance of several segments. A slight blunting of crude tactile sensation may occur, probably due also to pressure on the spinothalamic

tact Tactile localization, muscle-joint sense and vibratory sensation, all carried in the posterior columns of the cord, are unaffected. Because of the atrophy and *dissociated* sensory changes, this syndrome is frequently attributed to intrinsic disease of the cord. Its true nature is seldom recognized unless the possibility of a ventral protrusion is considered in the differential diagnosis.

Syndrome of Nerve Root Pressure—In a third group of cases the herniated nucleus is situated somewhat more laterally than in the other groups, compression being exerted not on the ventral column of the cord but on a nerve root near its emergence from the dura, with production of symptoms and signs referable to the root affected. Focal muscle

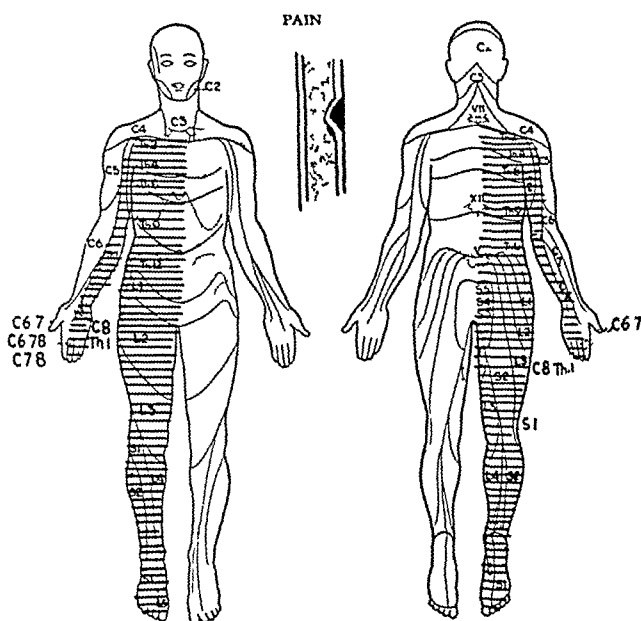


Fig 7—Sensory findings due to herniation of the nucleus pulposus between the fifth and sixth cervical vertebrae. The anatomic and sensory levels are not in agreement. The loss of pain and temperature sense is lower than the motor signs, which are at the level of the compression, this is due to the fact that the pain and temperature fibers cross obliquely in the spinal cord. The schematic insert was made along with the preoperative diagnosis of extradural pressure at the fifth segment.

atrophy and hypotonia limited to the distribution of the roots involved are found. The *sensory* signs are purely subjective, such as burning, gnawing and tingling sensations, which may be increased by movement of the extremity. Root pain and focal motor signs are the only diagnostic features. Lesions of this group are rare, and the clinical findings more closely resemble those associated with lumbar herniations, the picture being one of compression of a root alone and not compression of the spinal cord.

Comment—Cervical herniations of the nucleus pulposus may thus present three different syndromes. The first of these, the syndrome of bilateral pressure, may be subdivided into two entities, depending on the size and precise position of the projection. (a) If the mass is small and in the midline, bilateral pressure is exerted on the ventral horns of both sides and on both ventral roots, giving rise to bilateral signs referable only to the ventral gray columns, without other evidence of compression, (b) if the mass is larger, the signs are indistinguishable from those of a ventral tumor of the spinal cord. The second syndrome, that of unilateral ventral pressure, due to compression of the ventral



Fig 8—Unilateral extradural herniation of the nucleus pulposus compressing the seventh cervical root (From Stookey, 1928)

horn and ventrolateral columns of one side, consists of focal atrophy and crossed dissociated sensory changes, while the third, that of unilateral root pressure, is characterized by unilateral focal atrophy and focal pain without signs of involvement of the long fiber tracts. In the presence of any one of these syndromes it seems wiser, instead of accepting a diagnosis of intrinsic disease of the cord and the hopelessness which this implies, to do an exploratory laminectomy.

Vertebral tenderness is usually without diagnostic or localizing significance in cases of cervical disk protrusion.

Accentuation of symptoms following lumbar puncture, first mentioned as evidence of a spinal tumor by Elsberg and Stookey (1922),

is of only limited application in these cases. The significance of this test lies in the fact that withdrawal of the spinal fluid buffer between the mass and the cord accentuates the pressure on the latter, thus causing an increase in the signs already present and sometimes leading to the appearance of new ones. When, however, the mass is fixed to the long wall of the vertebral canal, as in these cases, displacement of the mass on removal of the fluid does not occur.

MANOMETRIC EXAMINATION

Evidence of spinal fluid block is seldom found in cases of herniation of the nucleus pulposus, since the protruded mass is rarely of sufficient size to obstruct the subarachnoid space completely. If a complete block occurs, the signs are usually so definite and the level so obvious that a diagnosis of neoplasm is far more likely to be made than one of herniation. With the smaller masses alterations in the dynamics of the spinal fluid are to be detected only by the most painstaking manometric studies. The jugular compression must be accurately timed with a stopwatch and the slightest alterations noted, such as a delayed rise or fall. Such alterations, carefully determined, are suggestive. Slight elevation in the total protein of the spinal fluid may be found but is not common.

INJECTIONS OF IODIZED OIL AND AIR

Because of the large amount of iodized oil found necessary to demonstrate herniation in the lumbar region, I have not felt it wise to use iodized oil in the cervical region, since the manipulations necessary to demonstrate alterations in the column may allow the fluid to enter the basal cisterns and even spread over the cerebral cortex, where it may remain, entrapped within the cranial cavity. Naffziger, Fleming and Jones found iodized poppyseed oil over the cerebral cortex in follow-up examinations of patients after the oil had been injected for the diagnosis of lumbar herniations. Such an occurrence would seem far more likely to follow the manipulations necessary to establish the diagnosis of a protrusion in the cervical region. Injection of air into the lumbar sac has been advocated by Stookey, Dyke and Scarff (1937) for the diagnosis of lumbar herniations, but this method has not been employed for cervical herniations since, as explained originally, it would require a complete, literally airtight block of the subarachnoid space to be of diagnostic value. With a compressive lesion of the cervical cord of this magnitude, the clinical evidence is so obvious that the test has not seemed necessary. In most cases the herniation is so small and discrete that it does not cause sufficient obstruction of the subarachnoid space to produce a manometric block, much less a block to passage of air.

If air is used in the diagnosis of cervical herniation, a sufficient amount must be injected to fill the cerebral ventricles and the cervical subarachnoid space. Thus, a combined encephalogram and myelogram

must be done. My associates and I have not had sufficient experience with this procedure in the rather rare cases of cervical herniation to estimate its value, though, if this condition is suspected and the signs are vague, the method is well worth trying, as we have done on occasion.

ROENTGEN EXAMINATION

In the original article on cervical lesions of this type it was stated that roentgen examination of the cervical column had given negative



Fig 9—Oblique roentgenogram of the cervical portion of the spine column showing calcified spurs (*S*) projecting into the intervertebral foramen, producing narrowing of the intervertebral foramen and compression of the emerging nerve root.

results in my cases. At that time the significance of a narrowed intervertebral space was not appreciated, and though a careful search was made for projections into the intervertebral foramina, oblique stereoscopic plates designed to show the intervertebral foramina were not made. Narrowing of the disk space between the fifth and sixth cervical vertebrae and between the seventh cervical and first thoracic vertebrae is often encountered, even when no signs of herniation of the disk are

present This sign is of value, therefore, only when accompanied by definite neurologic signs suggestive of one of the syndromes of compression Oblique stereoscopic plates have proved useful in ruling out the presence of spurs projecting within the intervertebral foramina and causing compression of the root at the foramen clinically indistinguishable from that within the vertebral canal due to laterally placed protrusion Occasionally, calcification in the herniated nucleus may be noted, and bony spurs projecting into the vertebral canal may be seen

OPERABILITY AND RESULTS

The end results of operations for cervical herniations are not as encouraging as those of operations for spinal neoplasms, removal of which is followed by rapid return of function and, on the whole, rather brilliant results Possibly, if the results were compared only with those of operations for ventral extradural tumors, the disparity would be less Removal of ventral extradural protruded masses is especially difficult owing to their relative inaccessibility and to troublesome bleeding from the extradural venous plexuses when the dura along the ventral part of the canal is cut to expose the herniation Masses firmly adherent to the underlying vertebrae are, moreover, more difficult to remove than soft tumors without firm attachments In several cases, because of ossification of the protruded mass, only partial removal could be accomplished but in others the mass could be removed completely Recovery of function took place, however, more slowly and was not as complete as following removal of a tumor of the spinal cord Such delay in recovery may be due in part to the fact that the lesion is hard and relatively sharply discrete and in part to the fact that the diagnosis is probably made in the majority of instances only after the lesion has been in existence a considerable time Compression under these circumstances is likely to produce a more permanent degenerative change in the spinal cord than occurs as a result of the less circumscribed and more easily recognized soft tumor

Another factor militating against complete recovery is incompleteness of removal In view of the nature of the protrusion and of its source it seems possible that additional material may protrude when movements of the neck are again resumed While it is not known that this takes place, it is conceivable that it does Chamberlain and Young (1939) reported the observation by Dr Temple Fay of alterations in the amount of protrusion in the lumbar region on flexion and extension of the spine during operation

Type of Laminectomy—Having tried both bilateral laminectomy and hemilaminectomy in the approach to the ventral surface of the spinal

cord in the cervical region, I feel that hemilaminectomy as introduced by Alfred S Taylor (1910) is the operation of choice, especially when the mass lies somewhat to one side of the cord as it most frequently does in this region. In hemilaminectomy the arches are removed farther ventrally and laterally than in bilateral hemilaminectomy, and a more

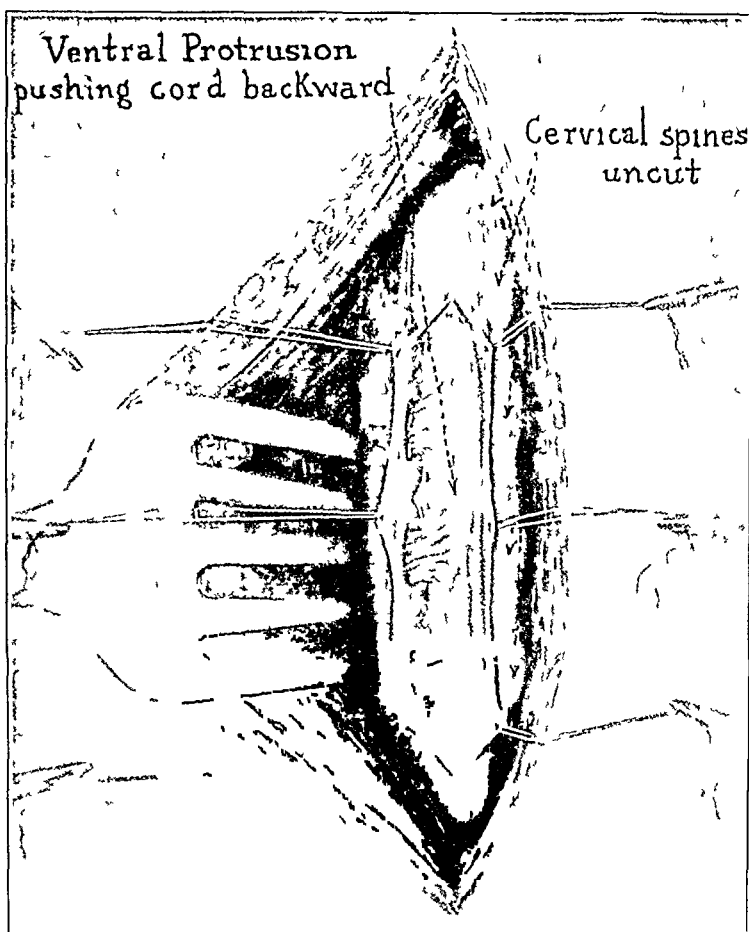


Fig 10—Hemilaminectomy with exposure of the cervical cord, according to the technic of Alfred S Taylor. This is the operation of choice for extradural ventral herniation of the nucleus pulposus. The arches on the left side of the vertebrae have been removed as far as the articular processes. The vertebral spines, the interspinous ligaments and the vertebral arches on the right side have not been disturbed. The dura on the right has been opened and retracted. A slight dorsal angulation of the cord due to ventral herniation of the nucleus pulposus is noted. (From Stookey, 1928.)

direct approach to the ventral surface is thus afforded. As bleeding is encountered when an extradural approach is made, this route is usually avoided in the cervical region. Furthermore, when the cord

is rotated, its visualization is advisable in order to avoid injuring it, as retraction of the cord with the dura unopened may lead to a greater trauma than occurs when the cord is exposed. When the protrusion is markedly lateral, however, sufficient retraction can be accomplished without opening the dura to permit removal of the herniated portion without trauma to the cord. Taylor's hemilaminectomy offers the further advantage that it disturbs the relationships of the vertebral column less than bilateral laminectomy. This is of special importance,

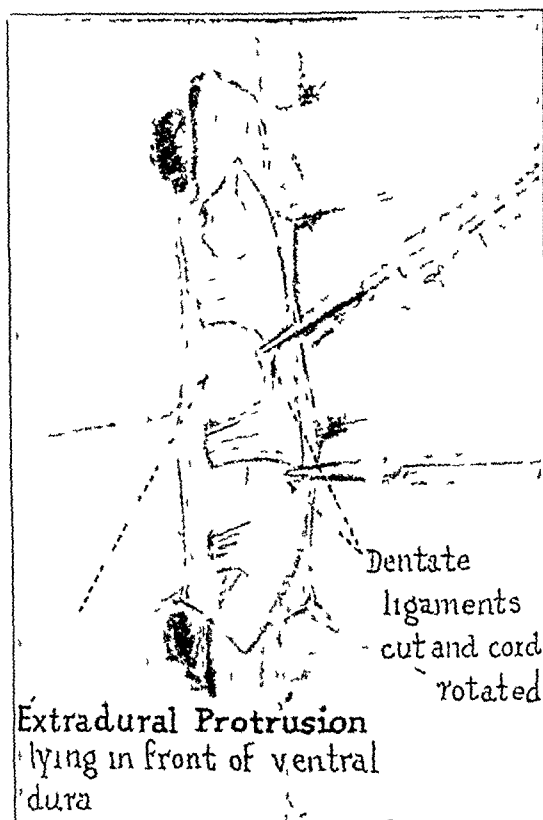


Fig 11—Same as figure 10. Two dentate ligaments have been cut, and the cord has been rotated, the ventral surface of the dura being brought into view. A ventral extradural herniation is seen beneath the dura. A longitudinal incision in the dura should be made over the herniation. (From Stookey, 1928.)

since the stability of the vertebral column may already be altered by the changes in the relations of the vertebral bodies and the intervening intervertebral disks found in herniations.

When the dura is opened and the cord brought into view, one or two dentate ligaments are grasped with mosquito forceps and cut to allow rotation of the cord and retraction to permit adequate exposure of the ventral aspect of the dura. A paramedian incision of 1 to 2 cm

is made in the ventral dura over the protruding portion of the nucleus pulposus. The protruding part can then be removed in pieces, usually in the form of thin layers of frayed cartilaginous tissue. After this removal, a depression having a relatively smooth base can be seen on the ventral surface of the vertebral bodies. The ventral opening in the dura is then sutured with one or two fine silk sutures.

If the protruded portion is large and extends across the midline, the opposite arches of one or two vertebrae immediately overlying the herniation may be removed, the hemilaminectomy being converted into a *local* bilateral laminectomy. Another paramedian incision is made in the dura on the opposite side, after rotation of the cord, and the herniated part of the disk is removed in the same manner. An approach from the opposite side will seldom be necessary.

SUMMARY

The so-called ventral extradural cervical chondroma, first recognized as a clinical entity in 1928, is now believed to be not a neoplasm but rather a portion of the nucleus pulposus protruding through the annulus fibrosus into the vertebral canal.

Such protruding parts exert pressure on the cord or nerve roots on both and give rise to three distinct syndromes: the syndrome of bilateral ventral pressure, the syndrome of unilateral ventral pressure, the syndrome of nerve root pressure.

Diagnosis of this lesion is frequently difficult, as the signs and symptoms may closely resemble those of intrinsic disease of the cord. This should be ruled out in selected cases by exploration rather than accept the hopeless outlook which such a diagnosis implies.

In the author's experience no approach gives as adequate an exposure as Taylor's hemilaminectomy for removal of herniated portions of the nucleus pulposus in the cervical region.

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CLINICAL ASPECTS OF PROTRUDED INTER- VERTEBRAL DISK

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Posterior protrusion of the intervertebral disk, an entity brought to attention by Mixer and Barr,¹ who recognized the value of employing radiopaque oil as a diagnostic means, has taken its place with other pathologic conditions producing backache and sciatic pain

I do not wish to imply that all posterior protrusions produce symptoms, however, a protrusion of sufficient size, advantageously placed, may produce pathologic changes in the nerve roots or the cauda equina sufficient to convince the most skeptical of its clinical significance

The present study was undertaken in an attempt to present the clinical findings in a series of cases in which definite neural changes were noted at the time of exploration and removal of a posteriorly protruded intervertebral disk

This group is composed of cases in which operation was performed at the Mayo Clinic in 1936 and 1937 All questionable cases and all cases in which no definite pathologic changes were demonstrated in the nerve roots or in the cauda equina at the time of operation have been excluded Operation was carried out by the neurosurgical staff

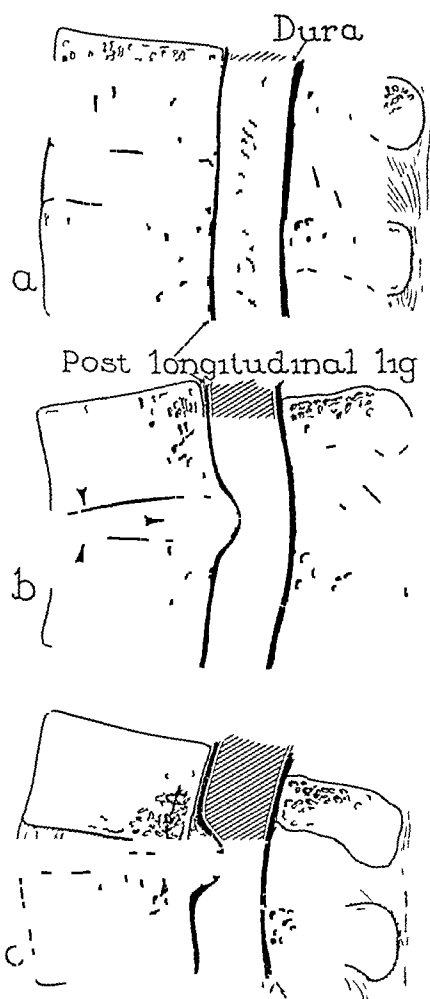
ANATOMY AND MECHANISM OF PRODUCTION

The intervertebral disk, or fibrocartilage, is composed of the annulus fibrosus and the nucleus pulposus The annulus fibrosus is composed of laminae of fibrous tissue and fibrocartilage and is so placed at the anterior and posterior intervertebral spaces as to confine the nucleus pulposus between the vertebral bodies The nucleus pulposus, a soft, elastic mass of fibrous tissue, is confined superiorly and inferiorly by the cartilaginous plate covering the inferior and superior portions of the vertebral bodies and anteriorly and posteriorly by the annulus fibrosus It is confined under pressure and acts in the capacity of a shock absorber, or cushion, for the vertebral bodies

From the Section on Orthopedic Surgery, the Mayo Clinic

¹ Mixer, W J, and Barr, J S Rupture of the Intervertebral Disc with Involvement of the Spinal Canal, *New England J Med* **211** 210-215 (Aug 2) 1934

The nucleus pulposus, normally circular, changes in shape under pressure, and there is a corresponding change of the annulus fibrosus to compensate for the changing nucleus. There must of necessity be an accompanying change in the position of the vertebral bodies and an uneven compression. To produce posterior stretching of the annulus, force must be applied over the vertebral bodies with the spinal column



Diagrams showing (a) a normal intervertebral disk, (b) rupture of the fibers of the annulus fibrosus and extrusion of the nucleus, and (c) possible changes in the annulus fibrosus and nuclear content with hyperextension

in the position of flexion. The anterior aspect of the intervertebral space is narrowed, with corresponding widening of the interspace from the front to the back. There results a tensing of the posterior portion of the annulus with a posterior bulging from the shifting nucleus. If sufficient force is applied, there may result one of two changes: (1) an acute rupture of the posterior portion of the annulus, probably

occurring at one or the other of its vertebral attachments, with a release of its nuclear content and loss of compression, or (2) a gradual change in the posterior portion of the annulus by disruption of its fibers with a gradual loss of resilience and, finally, force sufficient to complete the rupture with escape of the nuclear content of the annulus. In the course of the gradual rupture there may be recurrent bulge producing recurrent symptoms (see accompanying illustration, *a* and *b*)

There is another structure to be considered in conjunction with a posterior protrusion. This is the posterior longitudinal ligament, which in the earlier phases of rupture of the annulus may prevent production of clinical symptoms other than transient backache. The posterior longitudinal ligament is thickened over the vertebral bodies, thins out as it extends laterally and becomes adherent to the fibrocartilage. By its elastic qualities it may temporarily restrain the ruptured annulus and nucleus and later become stretched, thus permitting the characteristic bulge of a posterior protrusion in a lateral aspect. The anatomic structure of the posterior longitudinal ligament probably accounts for the unilateral nature of this syndrome, which may occur on either side and at more than one level, however, protrusions in the midline can occur. More correctly speaking, they are probably bilateral protrusions.

PATHOLOGIC PICTURE

The pathologic picture of a posteriorly protruded disk is that of nerve compression (by nerve compression I mean that the protrusion has compressed a root laterally and posteriorly against the pedicle of the vertebra and on the ligamentum flavum) from a ruptured annulus fibrosus, an extruded nucleus or a combination of the two. From the pathologic examinations in 100 cases forming the basis of this study, the predominant finding was degenerating fibrocartilage. In this series of cases only 15 per cent of the specimens showed remnants of notochordal tissue, and in a few instances degenerating hyaline cartilage was noted. Thirty-seven per cent of all specimens showed evidence of edema. This fact has been offered by Deucher and Love² as a possible explanation for the recurrent attacks of sciatic pain with repeated injuries.

The pathologic appearance at operation is that of a firm, hard protrusion at the posterolateral intervertebral space. On exposure by incision of the posterior longitudinal ligament, this protrusion may be seen to extrude itself into the wound, or it may be found firmly adherent, necessitating excision for its removal. Not infrequently,

² Deucher, W. G., and Love, J. G. Pathologic Aspects of Posterior Protrusions of the Intervertebral Disks. *Arch. Path.* 27: 201-211 (Feb.) 1939.

degenerating, cheeselike material is seen to extrude on incision of the lateral attachment of the posterior longitudinal ligament. There may also occur, though rarely, extrusion into the canal of several fragments, which are fibrous particles of the nucleus pulposus. It would appear from the anatomic and pathologic pictures that the presenting tumor in this syndrome is due to protrusion of the nucleus covered by the annulus fibrosus which has undergone fibrous changes. There may be an occasional case in which fibrous fragments of the dislodged nucleus become so placed as to produce nerve compression.

CLINICAL HISTORY

The clinical history resulting from a posterior protrusion with accompanying neural irritation commonly follows one of two patterns. 1 There may be recurrent "low backache," with the initial onset attributed to an injury severe enough to be remembered. There also may be an association of repeated injuries with an acute onset of sciatic pain following an apparently trivial injury, such as slipping, tripping or falling in a sitting position, in which there occur sudden flexion and torsion of the spinal column. The sciatic pain may be continuous or recurrent. There may be an associated paresthesia, which is commonly complained of in the form of numbness, tingling or needle-like pains over the buttock, the posterior aspect of the thigh, the posterolateral aspect of the leg or the dorsum of the foot. 2 There may be backache and sciatica together, continuous and with or without a history of remembered injury. The injury is frequently trivial and seemingly insufficient to cause an acute rupture of the annulus fibrosus. In this type, paresthesia is also a common complaint. In the presence of persistent sacral pain without disturbance of the achilles tendon reflex, posteriorly protruded disk at a high level should be suspected.

The sciatic pain is aggravated by activity, coughing, sneezing and motions which induce traction on the nerve roots. On close questioning regarding relief with rest, it is found that most of the patients become free from pain by lying absolutely immobile and that any motion reproduces the pain. Many positions may be assumed, the most common of which is lying on the side with the spinal column and the thighs flexed. From this clinical picture there may be many variations, such as relief on walking or standing and pain only in the buttock, thigh or leg. There are varied levels of pain and anesthesia. The effect of traction on the extremities varies: in some cases the sciatic pain is intensified and traction is intolerable, while in others it gives temporary relief, the pain recurring when activity is allowed. There are other cases in which traction affords periods of complete relief.

CLINICAL DATA

Group A—Of 100 cases studied, there was a history in 23 of injury severe enough to initiate symptoms unquestionably attributable to the injury

Group A-1—In 9 cases of this group, backache and sciatica occurred together, in 7 these symptoms were continuous, and in 2 they were recurrent

Group A-2—In 2 of the 23 cases there was continuous sciatic pain alone

Group A-3—In 12 of the group of 23 cases there was a history of many years of backache with late onset of pain over the distribution of the sciatic nerve. In 7 of these 12 there had been recurrent attacks of sciatic pain without a history of secondary injury to produce the onset of the sciatic pain, and in 5 cases there had been recent and persistent sciatic pain associated with a secondary minor injury

It was of interest to note that in 17 of the 23 cases the injury was sustained with the spinal column in a position of flexion and torsion, in the other 6 the posture was not known

Group B—In 9 cases of the group studied, there was a history of many years of backache without known injury to produce the symptoms. In all of these cases the onset of sciatic pain occurred while the patient was doing some type of work which required standing with the spinal column in a position of flexion, such as shoveling snow or pitching hay, after which the pain was persistent

Group C—In 68 cases of the series, the patients did not remember any injury of sufficient magnitude to produce onset of the symptoms

Group C-1—In 12 of this group of 13 cases, the onset of backache and that of sciatic pain were simultaneous, and both symptoms were persistent, in 1 case there was continuous backache with recurrent sciatic pain. In 11 cases the symptoms had been present a comparatively short time (several months), and in the remaining 2 cases the duration was several years

Group C-2—In 13 of the 68 cases there had been recurrent backache and recurrent sciatic pain for many years, and in 9 of these there had been several months of continuous sciatic pain prior to the patient's admission to the clinic

Group C-3—In 34 cases there was a history of many months to many years of backache and, later, onset of sciatic pain which had persisted continuously. The average duration of backache was seven and nine-tenths years, and the range was from one to thirty years. The average duration of persistent sciatic pain was from three to six months

Group C-4—In 8 cases of the group of 68 there was a history of sciatic pain alone. In 2 of these 8 there had been continuous pain of three and four months' duration respectively, and in 6 there had been recurrent sciatic pain with an average duration of three years.

Comment—From the foregoing data it is readily seen how difficult it is to draw any definite conclusion other than that the syndrome may include the following manifestations: (1) recurrent backache and recurrent sciatic pain, (2) continuous backache and recurrent sciatic pain, (3) continuous backache and continuous sciatic pain, (4) continuous sciatic pain without backache or (5) recurrent sciatic pain without backache.

From the pathologic anatomy one must conclude that the protrusion results from an injury or injuries or possibly from disease, although so far as I know the latter has not been reported. The impression one gets in reviewing the cases is that injury is the basis of all posterior protrusions but that the degree of the injury or multiple injuries determines the clinical history and the clinical course of the syndrome.

With a severe injury there may be an acute rupture of the posterior portion of the annulus and a corresponding bulge of sufficient degree and so placed that continuous symptoms are produced. There may be a spontaneous rupture from an apparently trivial injury in a previously damaged annulus. Also, there is some mechanism whereby the pressure from this posterior protrusion on the nerve root is released, producing remissions between the attacks. The nature of this mechanism constitutes a problem for much speculation. Is there recurrent edema of the protrusion which produces intermittent pain? Is the posterior longitudinal ligament an agent in gradually lessening the protrusion following rupture of the annulus fibrosus, and does it further assist in reducing recurrent displacements of the annulus fibrosus? Does the nucleus pulposus produce recurrent sciatic pain by shifting in and out of its anatomic position between the vertebral bodies, or does the partially or wholly extruded nucleus displace the annulus fibrosus in such a manner that there is resulting compression of the nerve roots from the annulus? Is the intermittency of the symptoms dependent on reduction of the nucleus into its intervertebral space, thereby allowing anatomic reposition of the annulus?

Deucher and Love² have suggested that recurrent edema is probably the explanation for recurrent sciatic pain associated with posterior protrusion of the intervertebral disk.

In 82 of 100 cases relief was noted with rest, in some obtained simply by inactivity and in others produced by a particular attitude assumed on lying down, such as flexion of the affected thigh on the abdomen or lying on one side or the other. In 64 cases the patient complained of some type of paresthesia.

CLINICAL FINDINGS

In attempting to describe the clinical findings from which a diagnosis can be made a certain group of cases must be considered in which the findings are characteristic of posterior protrusion. From this picture there may be many variations, even in those cases in which little clinical evidence is presented at the time of examination and a diagnosis is made from the history and the positive findings as shown by radiopaque oil or air studies. Not infrequently in this group is seen the patient with a large posterior protrusion in a symptomatically quiescent state, and, as has been stated before, this presents one of the interesting questions raised of the syndrome, namely, why there is an interval of quiescence of symptoms.

Positive Findings—In 50 of the group of 100 cases, there was unilaterally limited "straight leg raising," in 24 there was a bilaterally limited "straight leg raising," and in 26 the patients were considered normal in this respect. In 17 cases there was atrophy of either the buttock or the extremity or both, 13 of these cases occurring in groups A and C-3.

Inspection—The characteristic position of the spinal column in the cases of acute involvement was a list to the unaffected side, with scoliosis of the lumbar vertebrae. This was noted in 33 of 100 cases. In only 5 cases was there a list to the affected side. In 24 cases the posture was good, in 21 cases no mention of posture was made, and one assumes that it was good. In 1 case there was alternating scoliosis, which is almost pathognomonic of a bilateral or midline posterior protrusion, however, there is commonly a bilateral protrusion without alternating scoliosis. In 16 cases there was obliteration of the lumbar lordosis with generalized flattening of the back.

Palpation—In 50 cases tenderness was elicited over the lumbosacral joint and was felt to arise from pathologic changes in this joint. Possibly in some cases the tenderness resulted from a lesion of the fourth and fifth lumbar interspace. In 50 cases tenderness could not be elicited on physical examination or was of such little significance that it was not noted. In 39 there was tenderness over the region of the sacroiliac joint on the affected side, which is probably of little clinical significance. In 80 cases, or 80 per cent, there was definite limitation of motion, particularly in flexion of the spinal column.

ROENTGEN EXAMINATION

Of 98 cases in which fluoroscopic examination with radiopaque oil was done, there were 93 in which a positive defect was found, 4 in which the procedure was a failure and 1 in which a protruded disk was found at the interspace between the fourth and fifth lumbar vertebrae.

at operation after the results of roentgen examination had been reported as negative. In the 2 remaining cases of the series direct exploration was carried out without roentgen examination. Camp³ reported that by the use of radiopaque oil accurate diagnoses have been made in 92.3 per cent of 210 cases observed at the Mayo Clinic. In view of the fact that radiopaque oil may give rise to radiculitis, air studies have been employed when advisable, and resort has been made to radiopaque oil when air studies failed to demonstrate a suspected lesion. Roentgen examination after injection of air into the spinal canal has been referred to by others as myelography. In the Mayo Clinic it is referred to as taking a spinogram and is employed as a means of diagnosing a protruded intervertebral disk.

Skeletal Changes—In 34 patients changes were noted on roentgen examination of the bony structures in association with the posterior protrusion, there were 1 with spondylolisthesis, 2 with "facet changes," 3 with hypertrophic changes and 28 with narrowing of the lumbosacral or the fourth and fifth lumbar interspace, all corresponding to the site at which the posterior protrusion occurred. Of this group of 28 patients, 13 were in group C-3, the group with many months to years of backache.

Location—Forty-one of the posterior protrusions occurred at the fourth and fifth lumbar interspace, 46 at the lumbosacral joint, 8 at the third and fourth lumbar interspace and 1 at the second and third lumbar interspace. Four patients showed multiple protrusions. Of this group there were 28 midline or bilateral protrusions of the disks. Each of the remaining 72 protrusions was unilateral.

Neurologic Examination—The most important finding in neurologic examination was the reporting of a diminished achilles tendon reflex, however, a normal reflex does not preclude the finding of a posteriorly protruded disk. In 66 of the group of 100 cases there was evidence of a diminished achilles tendon reflex. In 13 cases this was graded —1 on a basis of —1 to —4, in 8 cases it was graded —2, in 14 cases it was graded —3, and in 31 cases it was graded —4.

Of the group of 100 cases there were 12 in which there was bilateral sciatic pain and in which a bilateral protrusion was found. The findings in this series compare closely with those reported by Love⁴ and by Love and Walsh⁵ on different occasions, minor discrepancies resulting from the choosing of a small series of cases.

3 Camp, J. D. Personal communication to the author.

4 Love, J. G. Intractable Low Back and Sciatic Pain Due to Protruded Intervertebral Disks. Diagnosis and Treatment, Minnesota Med 21 832-838 (Dec) 1938.

5 Love, J. G., and Walsh, M. N. Protruded Intervertebral Disks. Report of One Hundred Cases in Which Operation Was Performed, J. A. M. A 111 396-400 (July 30) 1938.

TOTAL PROTEIN

The presence of high values for total protein in the spinal fluid has been of considerable importance in the neurologic examinations for intraspinal lesions, and one would anticipate an elevation of the value for this substance in the presence of a posterior protrusion of the intervertebral disk. This, however, was not always the case, the protein content of the spinal fluid has been found to be normal or at a low level in some cases in which a large posterior protrusion was present. The significance of the elevated value for protein in this syndrome is that it adds more positive evidence to that on the basis of which a lesion is already suspected. In cases in which clinical examination is not diagnostic and the results of neurologic examination are objectively negative, it may be a reason for proceeding with a more exhaustive study, including a roentgen examination of the spinal canal after injection of air or radiopaque oil. This may be particularly advisable for the orthopedist or the neurologist, who does not have ready access to fluoroscopic or roentgen facilities. In 4 cases of this group, estimation was not made, and in the other 96 cases the average protein content of the spinal fluid was 53.8 mg per hundred cubic centimeters. In 36 cases the protein content did not exceed 40 mg per hundred cubic centimeters. In 4 cases it was 45 mg. In the remaining 56 cases the protein content per hundred cubic centimeters of spinal fluid was more than 45 mg and was considered to be of definite pathologic significance. The highest protein content for any individual patient was 220 mg per hundred cubic centimeters of spinal fluid.

Average of Patients by Groups—Group A was found to have an average value for total protein of 45.5 mg per hundred cubic centimeters of spinal fluid. In 9 cases of group A, the value for total protein was normal, in 2 the value was 45 mg per hundred cubic centimeters of spinal fluid, in 3 no estimation was done. In the remaining 9 cases there was a definite increase above normal in the value for protein.

In group B there was an average value for total protein of 50 mg per hundred cubic centimeters of spinal fluid. In 4 cases the values for protein were normal. In the remaining 5 there was a definite elevation above the normal level.

In group C-1, the average value for protein was 58.5 mg per hundred cubic centimeters of spinal fluid. In 4 cases there were normal values, and in 9 there was an elevation above the normal level.

In group C-2, the average value for protein was 64.6 mg per hundred cubic centimeters of spinal fluid. In 3 cases there were normal values, in 1 the total protein was not estimated and in 1 there was a value of 45 mg. In the remaining 8 cases there was an elevation above the normal level.

In group C-3, the average value for total protein was 54.4 mg per hundred cubic centimeters of spinal fluid. There were normal values in 14 cases, in 2 there was a value of 45 mg, and in 18 there was an elevation above the normal level.

In group C-4 there were 8 cases in which sciatica was continuous. In 4 of these the value for total protein was normal, and in 4 it was elevated. The average value was 50 mg.

SUMMARY

This is an attempt to present the findings as noted on orthopedic examination and to a lesser extent on neurologic examination in 100 cases in which posterior protrusion of an intervertebral disk was of apparent significance in producing symptoms. It is felt that this syndrome presents sufficient clinical evidence in the history and the examination to arouse suspicion of a posteriorly protruded disk in practically all cases and that in the majority the condition can be diagnosed on the clinical history and examination alone. However, roentgen examination should probably be carried out on all patients to determine the location of the protrusion or protrusions. Also, there is a group of patients in the quiescent period for whom a roentgen examination is necessary for demonstration of a suspected lesion. There is still a third group, with the usual clinical findings and history, in whose cases the results of the roentgen examination are negative but must be considered in deciding whether to make an exploratory examination.

It is my impression after completing this study that a possible explanation of the intermittency of symptoms is that in some manner a change in position of the dislodged nucleus beneath the annulus fibrosus results in reduction to approximately normal anatomic position. From the cases observed at operation, one would anticipate that this could occur by reduction of a protruded nucleus pulposus between the intervertebral bodies, permitting a collapse of the annulus and a release of nerve compression.

I should also like to mention a test which is felt to be of significance in examination of patients with posterior protrusion, that of a sudden unexpected hyperextension at the lower lumbar vertebrae. When the result is positive, pain is reproduced over the course of the affected sciatic nerve. The mechanism whereby this occurs is probably a narrowing of the posterior interspace with a sudden relative increase in the posterior bulge, with sudden pressure on the nerve root (see illustration, C).

As regards the treatment of this lesion it is confined to the neurosurgical division of the clinic and consists of laminectomy and removal

of the ligamentum flavum and the disk, in which procedure the articular facets are preserved. There are many cases in which the consideration and aid of the orthopedist are required in association with the neurosurgical procedure, and it is essential to have close harmony between the orthopedist and the neurosurgeon in the handling of these cases. The cases in which a combined procedure is employed, that of hemilaminectomy and removal of the disk and bone grafting, include such conditions as spondylolisthesis, separated neural arch without slipping of the vertebral body and marked narrowing of the intervertebral space with hypertrophic arthritic changes.

Dr J W Kernohan reviewed the pathologic specimens. Members of the neurosurgical staff gave valuable suggestions and permitted access to the surgical notes.

IODIZED OIL MYELOGRAPHY

USE IN THE DIAGNOSIS OF RUPTURE OF THE INTERVERTEBRAL DISK INTO THE SPINAL CANAL

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BOSTON

Roentgen examination after the injection of iodized oil into the spinal subarachnoid spaces (iodized oil myelography) is the most important step in the diagnosis of rupture of the intervertebral disk into the spinal canal. The accurate roentgen localization of the lesion is of distinct value to the surgeon, and the demonstration of the mechanism by which the fragment of the ruptured disk presses on the cauda equina has added weight to the evidence that rupture of an intervertebral disk into the spinal canal is a definite clinical entity.

A positive diagnosis of posterior protrusion of an intervertebral disk into the spinal canal has been made at the Massachusetts General Hospital in 133 cases by the use of iodized oil, roentgenoscopy and instantaneous films taken during roentgenoscopic examination.¹ All except 9 of these diagnoses were proved correct at operation. There were 2 cases of negative results on roentgen examination with positive operative findings and 2 of questionable roentgen diagnoses with positive operative findings. A dilated arachnoid vein, a fractured pedicle, a small osteoma and in 2 cases a thickened ligamentum flavum were misinterpreted as ruptured intervertebral disks. Surgical exploration has been done with negative results in 9 cases, of which negative results were expected from roentgen examination in 7 and positive in 2. The accuracy of diagnosis is therefore 93 per cent.

Air myelography is rapidly coming into use in the diagnosis of rupture of the intervertebral disk.² The accuracy of this type of

1 Mixer, W J. Protrusion of the Lumbar Intervertebral Disks, read at the Fourth International Neurological Congress, Copenhagen, Denmark, Aug 24, 1939, other unpublished data.

2 Young, B R, and Scott, M. Air Myelography. The Substitution of Air for Lipoidal in Roentgen Visualization of Tumors and Other Structures in the Spinal Canal, *Am J Roentgenol* **39** 187-192, 1938. Dandy, W E. Ventriculography Following Injection of Air into Cerebral Ventricles, *Ann Surg* **68** 5-11, 1918. Coggeshall, H C, and von Storch, T J C. Diagnostic Value of Myelographic Studies of Caudal Dural Sac, *Arch Neurol & Psychiat* **31** 611-613 (March) 1934. Van Wagenen, W P. Roentgenological Localization of Spinal Subarachnoid Block by Use of Air in Subarachnoid Space, *Ann Surg* **99** 939-943,

(Footnote continued on next page)

examination varies considerably in the hands of different workers. Improvements will undoubtedly be made in the technic of this examination and the accuracy of roentgen interpretation, but at present it is doubtful that a positive diagnosis of rupture of the intervertebral disk can be made in over 50 per cent of the cases. Even if an error of 50 per cent in the diagnosis of rupture of the disk by air myelography persists, the procedure should nevertheless be used, as a preliminary, before the injection of iodized oil, because in that way it will probably be possible to eliminate the use of iodized oil and its questionable ill effects in one half of the patients. Air myelography is of distinct value when the findings are unequivocally positive, but it is of little value when the findings are equivocal or negative.

The indications and contraindications for iodized oil myelography have been discussed at length in the literature.³ It has been maintained that iodized oil may be safely injected into the spinal subarachnoid spaces if the procedure is properly carried out, but the indiscriminate use of this valuable method of diagnosis is to be avoided. The patient who is to be subjected to this examination should be carefully selected. There should be no doubt that he is suffering from a disease sufficiently disabling to warrant a major surgical procedure for relief. The discovery of a narrowed joint space by plain roentgenograms is not an indication for the examination with iodized oil. Even though this finding may indicate rupture of the disk there is no indication that it is pressing upon the cauda equina.

It cannot be too strongly emphasized that iodized oil in the spinal canal is a foreign body and remains as such for many years. Of over 200 patients subjected to this type of examination at the Massachusetts General Hospital, 4 have had fairly persistent untoward symptoms presumably developing from the use of iodized oil. Two complained of headaches coincident with the lodgment of the iodized oil in the cranial

1934 Camp, J. D. The Comparative Value of Subarachnoid Air Versus Lipiodol in the Diagnosis of Intraspinal Protrusion of the Intervertebral Disks and of Hypertrophy of the Ligamentum Flavum, read at the Fortieth Annual Meeting of the American Roentgen Ray Society, Chicago, Sept. 21, 1939.

3 Mixer, W. J., and Ayer, J. B. Herniation or Rupture of the Intervertebral Disk into the Spinal Canal, *New England J. Med.* **213** 385-393, 1935. Harkins, H. N. Use of Iodized Poppy Seed Oil in Differential Diagnosis Between Tumors of Conus Medullaris and of Cauda Equina, *Arch. Neurol. & Psychiat.* **31** 483-503 (March) 1934. Globus, J. H., and Strauss, I. Intraspinal Iodology. Subarachnoid Injection of Oil as Aid in Detection and Localization of Lesions Compressing Spinal Cord, *ibid.* **21** 1331-1396 (June) 1929. Mixer, W. J., and Barr, J. S. Rupture of the Intervertebral Disk with Involvement of Spinal Canal, *New England J. Med.* **211** 210-215, 1934. Barr, J. S., Hampton, A. O., and Mixer, W. J. Pain Low in the Back and Sciatica Due to Lesions of Intervertebral Disks. *I. A. M. A.* **109** 1265-1270 (Oct. 16) 1937. Lindblom, A. F. On the Effects of Various Iodized Oils on the Meninges, *Acta med. Scandinav.* **76** 395-402 1939.

vault One complained of pain referable to a dorsal root and another of coccygodynia In 1 of the patients suffering with headaches the oil was caused to enter the cranial cavity by placing the patient in the Trendelenburg position for treatment of shock This patient had had three times the usual quantity of oil injected, and it had been incompletely removed In the other patient headache followed the roentgenoscopic examination, at the time of which the oil was caused to enter the cranium There are other patients in the group who have oil in their cranial vaults without any symptoms, but, since the oil cannot be dislodged from the cranial subarachnoid spaces or ventricles, great care should be taken to prevent it from entering those areas The patient should be instructed not to stand on his head until the oil has been removed

If the patient has had a previous subarachnoid injection of air it is advisable to withhold injection of oil until the air has completely disappeared and normal spinal fluid pressure has returned, because collapse of the subarachnoid space or retention of air prevents the free flow of iodized oil during roentgenoscopic examination, and this may cause multiple false filling defects A previous lumbar puncture for studies of the spinal fluid may result in a leak of spinal fluid which interferes with the examination The difficulties and dangers of injecting the oil when a free flow of spinal fluid is not obtained are obvious Several instances of subdural and extradural injections of iodized oil have occurred under these circumstances and also even when a free flow of fluid was present The oil should be heated before injection to reduce its viscosity, which makes it difficult to maintain the point of the needle in the subarachnoid spaces while the pressure required to empty the syringe is applied Care should be taken to select fresh iodized oil This can be determined by the date marked on the ampule and also by the color of the oil Fresh iodized poppyseed oil is practically colorless, but when deterioration occurs it becomes amber or yellow It is difficult to determine slight changes in color unless a fresh ampule is available for colorimetric comparison There is a definite variation in the reaction of the patient to the injection of iodized oil into the subarachnoid spaces It would appear that there must be some difference in the oil itself Some patients have no symptoms, while others have fairly severe transient reactions, but, as has been stated these reactions are seldom persistent The reports in the literature of persistent untoward reaction have originated from sources where iodized oil is used infrequently and this suggests that old or deteriorated oil may have been used It is necessary to inject 4 to 5 cc (one ampule) of iodized oil into the subarachnoid spaces in order to allow a satisfactory roentgen examination Smaller quantities have been tried, and errors were common unless the

spinal fluid was blocked. The roentgen examination can be done at any time after the injection of iodized oil, because it remains freely movable even after several years. Most of the roentgen examinations are made on the same day as iodized oil is injected. The only contraindication for the immediate examination is the infrequent occurrences of a "lumbar puncture headache." On the day after the injection, the patient may be more uncomfortable, and it may be necessary to give appropriate drugs for the relief of pain so that the patient may be more able to cooperate in the examination.

ROENTGEN TECHNIC FOR IODIZED OIL MYELOGRAPHY

Since over 90 per cent of ruptures of the intervertebral disks which produce pressure on the spinal cord or cauda equina occur in the lumbar area, only the technic of examination of this area will be discussed. For the complete examination of the lumbar subarachnoid spaces with iodized oil it is necessary to use a tilting motor-driven roentgenoscopic table. It is possible, however, to obtain a fairly satisfactory examination of the areas of the fourth and the fifth lumbar intervertebral disk by using a horizontal roentgenoscopic table. A quick change-over switch which allows instantaneous exposure of films during the roentgenoscopic examination is necessary in either case. The purpose of the examination is to demonstrate a small, anteriorly placed, unilateral, extradural pressure defect in the subarachnoid spaces. Since 5 cc of iodized oil fills only a small portion of the subarachnoid spaces, it is necessary to cause this oil to pass up and down the spinal canal over the areas of the disks. The oil used is of the "heavy" type and consequently gravitates posteriorly when the patient is supine and anteriorly when the patient is prone. Because of the small amount of oil and the effect of gravity, it is necessary to examine the patient in all positions in order to rule out a small extradural defect, but when searching for a ruptured intervertebral disk it is usually necessary to examine the patient only face down, or prone, as the oil crosses the area of each disk. An effort should be made to have the maximum amount of oil occupy the level of each disk, i. e., maximum filling opposite each intervertebral disk must be obtained before it is possible to rule out disease. The examination is begun with the patient facing the fluoroscopic table in the upright position. In this position all the iodized oil is in one mass and occupies the sacral cul-de-sac. In some patients the upper level of the oil may reach the middle of the fourth lumbar vertebra, but in the average patient the oil barely reaches the level of the fifth disk. The anteroposterior view, both the oblique views and the lateral view of the column of iodized oil are taken with the patient upright if the oil extends above the level of the fifth disk. It is necessary to take films as the oil occupies the

level of each disk, because some of the filling defects are too small to be visualized with the fluoroscope. This is particularly true with unilateral rupture of the fifth lumbar disk. The patient is then slowly brought to the horizontal face-down position, and just before it is reached the iodized oil usually occupies the area of the fourth disk. Roentgenoscopic observations are made, and four views of the spine are repeated. The patient is then further manipulated, to the Trendelenburg position, and as the oil crosses the area of each disk, observations are made and films are taken. If examination of the spinal canal for lesions higher than the second lumbar disk is desired, it is necessary to place the head of the patient at the foot of the table, because the extreme Trendelenburg cannot be obtained when the patient is in the opposite position. The height to which the examination is carried will of course depend on the suspected level of the disease, but in all cases of sciatica the examination should be carried to the tenth or eleventh dorsal vertebra. The entire cauda equina and the conus medullaris should be completely examined. It will be noted that when the head of the prone patient is lowered to the extreme Trendelenburg position the flow of iodized oil will slow down as it reaches the conus medullaris. This slowing down of the oil is due less to the sudden change in the size of the structures of the spinal canal than to variation in its curve. The anterior lordotic curve of the lumbar spine reverses to the kyphotic curve of the dorsal spine, thus the incline of the oil is changed. In addition to the delay often noted at the conus medullaris, there is a tendency for the oil to break into small globules, and these may split into one or two streams flowing down one or both sides of the canal. An attempt should be made to prevent this breaking up of the oil by reducing the angle of the Trendelenburg position. It is obvious that particles of iodized oil may pass around small filling defects, whereas the bolus or mass of the entire amount would show these defects well. The small droplets can be brought together as one mass by simply bringing the patient to the upright position. If the dorsal or cervical areas are to be examined, it is important that the oil be carried toward the cranium with the patient lying prone on the table and the cervical spine held in extreme hypertension. The head can be maintained in this position by placing pillows underneath the chin. It is important that the position be maintained, especially when the oil enters the cervical area to prevent the oil from reaching the cranial cavity. The patient should not be placed in a more nearly vertical position than is necessary to cause the oil to flow toward the head, because, even with the neck in extreme hyperextension, the oil will sometimes flow into the cranial cavity. If during the progress of the iodized oil from the sacrum to the cranium, apparent filling defects are noted, an effort should be made to obliterate them by manipulation of the oil upward and downward.

and from side to side. The filling defect must be constant. Often the oil will separate into an hourglass shape as it crosses the levels of the disks, particularly in the lower dorsal and upper lumbar areas. A symmetric, smooth hourglass shadow is rarely due to rupture of the intervertebral disk. It is more likely due to a sudden change in the angle of the incline of the flow of iodized oil, the hourglass shape of the oil being due to both the viscosity of the oil and the difference in the rate of flow of the upper and lower halves of its mass. Hourglass constrictions can be made to disappear as the rate of flow of the entire mass of iodized oil is increased by a more rapid increase in the angle of descent. The physical principles involved may be compared to that involved in pouring thick liquid out of a small-mouthed vessel or in the stretching and separation of taffy candy. The extent and degree of any filling defect is of course best demonstrated when the maximum amount of oil is in contact with it.

It must be borne in mind that complete filling of the spinal subarachnoid spaces at any level except in the sacral cul-de-sac is impossible. When the patient is face down the oil gravitates toward the anterior aspect of the spinal canal and has a relatively shallow level. When the patient is on his back all the oil gravitates to the posterior aspect of the canal and again finds a level. If the entire canal is to be examined it is necessary that the patient be rotated in all positions under roentgenoscopic observation and the flow of the iodized oil observed in these positions. Fortunately, ruptures of the lumbar intervertebral disks are nearly always visible when the patient is examined in the face-down position with the oil equally divided above and below the involved disk. In some cases filling defects due to ruptured disks are so small that they are seen only in the oblique view, and even more rarely the lateral view is of benefit. When the defect is seen only in the lateral view it is seldom of clinical importance.

THE CHARACTERISTIC IODIZED OIL DEFECT

It is beyond the scope of this paper to include a complete roentgen description of the mechanism and variations in the filling defects produced by ruptures of the intervertebral disk. Robinson and I have already done this in our original presentation,⁴ which has been confirmed by others. Only typical examples of each type of ruptured disk in the lumbar area are herewith presented.

4 Hampton, A. O., and Robinson, J. M. The Roentgen Demonstration of Rupture of the Intervertebral Disk into the Spinal Canal After the Injection of Lipiodol, with Special Reference to Unilateral Lumbar Lesions Accompanied by Low Back Pain with "Sciatic" Radiation, *Am J Roentgenol* **36** 782-803 1936.



Fig 1—Drawing of the normal lumbar subarachnoid space filled with iodized oil. This is a composite of numerous roentgenograms, and the nerve roots are drawn in their anatomic locations.

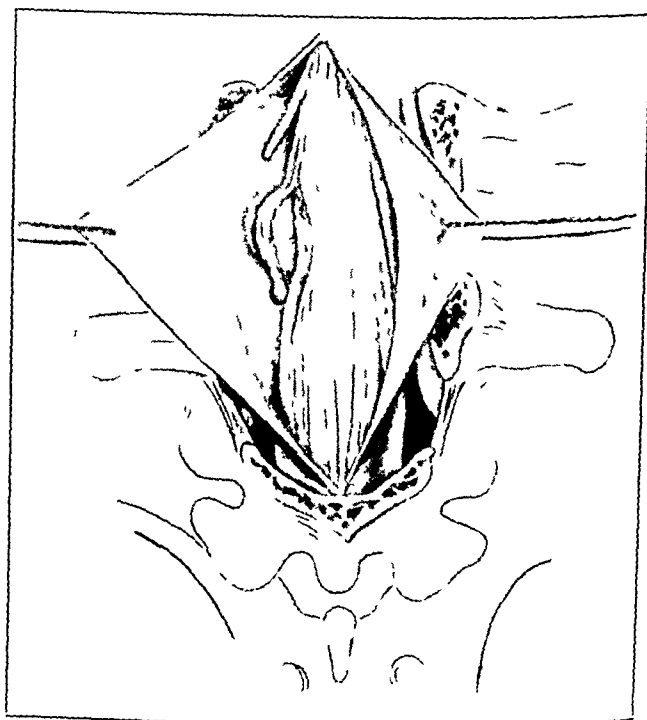


Fig 2—Rupture of the fourth lumbar disk exposed by opening the dura.

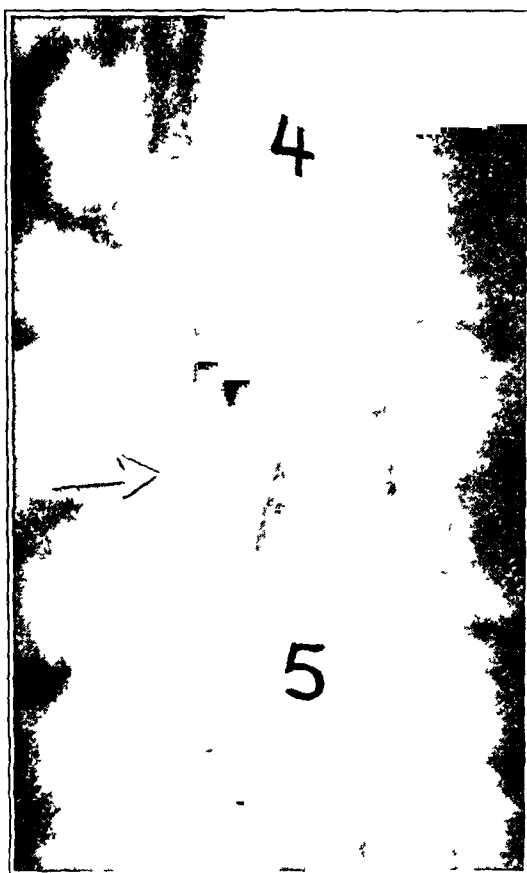


Fig 3—The characteristic filling defect of unilateral rupture of the fourth lumbar disk



Fig 4—The most common filling defect produced by unilateral rupture of the fifth lumbar disk



Fig 5—Failure to demonstrate rupture of the left side of the fifth lumbar disk



Fig 6—Comparison of an air (A) and an iodized oil (B) myelogram Rupture of the fourth lumbar disk extends across the midline

Figure 1 illustrates the normal lumbar subarachnoid spaces when completely filled with iodized oil. The course of the nerve roots has been drawn in, and each is labeled. Asymmetric filling of the root sheaths is a normal variation. It should be noted that the first sacral nerve crosses the fifth lumbar disk outside of the shadow of the iodized oil and that it is therefore possible for a rupture of the fifth lumbar disk to press on the root of the first sacral nerve without its being demonstrable by myelography. All the other nerves of the cauda equina cross the area of the disk within the shadow of the iodized oil, and for this reason pressure on these roots by a ruptured disk should always be demonstrable.

Figure 2 illustrates the mechanism of the filling defect produced in the subarachnoid spaces at the level of the fourth disk. Note that the lesion is in an anterolateral position, is about 1 cm in diameter and elevates and displaces the more lateral nerve roots. Such ruptures of the fourth lumbar disk always press on the root of the fifth lumbar and perhaps on the first sacral nerve.

Figure 3 illustrates typical rupture of the fourth disk. The serrated upper margin corresponds to the compressed roots of the fifth lumbar and the first sacral nerve. It should be noted that the defect begins at the inferolateral margin of the lamina of the fourth lumbar vertebra, being adjacent to the posteroinferior articulating facet (compare fig 2).

Figure 4 illustrates a typical rupture of the fifth lumbar disk. As has been pointed out, such defects are smaller, because the iodized oil-containing area does not extend as far laterally as the mass of the ruptured disk.

Figure 5 is a normal myelogram of the areas of the fourth and the fifth lumbar disk, but a rupture of the fifth lumbar disk was found at operation. There have been 2 such examples in the present series of cases.

In figure 6*A* air has been injected into the lumbar subarachnoid spaces and a filling defect is demonstrated opposite the fourth lumbar disk. This filling defect is indistinct and does not show the characteristics of the iodized oil myelogram (fig 6*B*).

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INTRASPINAL PROTRUSION OF INTER- VERTEBRAL DISKS

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PROTRUDED INTERVERTEBRAL DISK WITH COMPRESSION OF NERVE ROOT AND SPINAL CORD

Since the syndrome of protruded intervertebral disk became established, it has been diagnosed more and more frequently, not alone by the neurologist and orthopedist but by the general practitioner. It has been only within the last few years that a clinical diagnosis could be made of posterior protrusion of an intervertebral disk into the spinal canal, with subsequent compression of the spinal cord or of one or more nerve roots, and yet today it is a diagnosis that can be made in a high percentage of cases by any up-to-date physician. The information which has been collected, analyzed and correlated in the clinics of this country and given freely to the medical profession, by means of publications in medical journals and lectures before medical societies, has served to alleviate a great deal of suffering and to restore many workers to their former fields of usefulness after more or less prolonged periods of disability. The economic saving in time and money is inestimable.

For the sake of argument one might ask if there is not an increase in the number of persons who are undergoing operation for a condition that a few years ago was treated mostly by nonoperative methods. It is our feeling that this is definitely true. We also feel that the change in treatment, founded as it is on sound anatomic, pathologic and surgical principles, is fully justified, and further, since the patients in carefully studied and selected cases are restored within a relatively short time to useful activity by the employment of the proper surgical treatment, there seems to be no justification for the older methods of so-called conservative treatment, which have to be carried on indefinitely, with a period of two weeks to three months of rest in bed either at home or in a hospital every year.

From the Section on Neurosurgery (Dr Love) and the Section on Neurology (Dr Walsh), the Mayo Clinic

Immediately, we wish to emphasize that we strongly favor and urge a trial period of so-called conservative treatment, unless there is gross evidence of damage to the central nervous system, before the undertaking of neurosurgical methods for the relief of pain in the neck, shoulders, back or lower extremities. A period of observation on conservative treatment will indicate to the careful observer, in many cases, that there is an underlying lesion of the spinal cord or of a nerve root which must be attacked centrally.

We are still convinced that the intervertebral fibrocartilaginous disks protrude posteriorly into the spinal canal as the result of unusual stress or strain applied to the vertebral column. This stress may be the result of a single outstanding injury or it may be the result of repeated injuries of varying degrees of severity.

In an analysis of 500 consecutive cases in which operation was performed at the Mayo Clinic for protrusion of one or more intervertebral disks, we have learned that 58 per cent of the patients gave a history of a specific injury to the back. Many patients, when they give their history for the first time, fail to mention any past injury, however, when more closely questioned regarding accidents and injuries many of them recall some episode followed by backache which subsided after a reasonable length of time. Most of these persons had not connected their presenting chief complaint of backache or sciatic pain with the injury. This is true particularly if there has been a long interim of freedom from pain. An analysis of our series of cases brings out the point to which we have called attention previously, that a high percentage of patients give a history of intermittency of symptoms. Eighty-four per cent of our 500 patients had intermittent symptoms. Whether this intermittency is due to vascular changes in the protruded portion of the disk as suggested by Deucher and Love¹ or to degeneration and interruption of pain fibers as a result of compression of the nerve root by the protruded body as suggested by Adson² or to a return of the protruded fragments to within the center of the intervertebral space, as has been suggested by many, is not known. That intermittency is a characteristic finding in these cases is noteworthy, and it serves as a useful criterion in distinguishing between root pain caused by a protruded disk and that caused by an intraspinal neoplasm, which usually is marked by definite progression of symptoms and signs.

1 Deucher, W. G., and Love, J. G. Pathologic Aspects of Posterior Protrusions of the Intervertebral Disks, *Arch. Path.* **27** 201-211 (Feb.) 1939.

2 Adson, A. W. Personal communication to the authors.

Protrusion of any intervertebral disk may occur, as far as we know, but in the vast majority of cases the protrusion occurs in the lumbar region of the spinal canal. Approximately 96 per cent of our 500 patients had lumbar protrusion (fig 1). This is an important fact which helps to make an otherwise extremely complicated problem comparatively easy to solve.

Protrusions in the cervical and thoracic regions of the spinal canal because of the limited amount of space between the spinal cord and the bony canal, resemble more closely intraspinal neoplasms, and they are usually detected more promptly than those in the lumbar region where the cauda equina has such freedom of motion. No lesion can

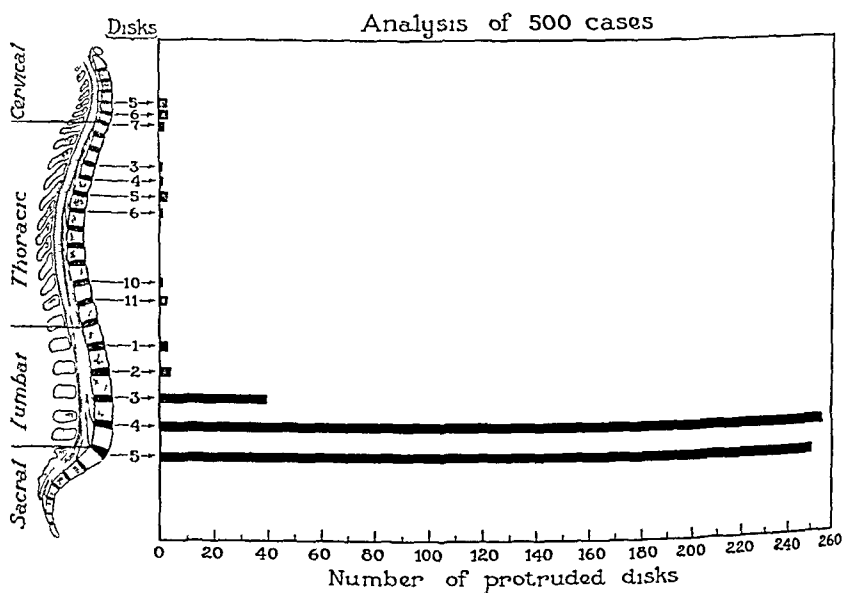


Fig 1—Frequency of protrusion of intervertebral disks at various levels in the spinal column

assume much size in the cervical and thoracic regions of the spinal canal without interrupting some nerve pathway and thus calling attention to a compressive lesion. However, in the lumbar region a mass may be large before any conduction system is affected.

Men, it would seem, are more unkind to their backs than are women. In our series there were 358 men and only 142 women who were operated on because of protruded disks. This cannot be taken, we feel, to indicate that the male's back is weaker than that of the so-called weaker sex. It means probably that the discrepancy is due to the etiologic factor, trauma, which has a greater chance to exert itself among men, who ordinarily do most of the heavy lifting and straining.

and who, in industry, are more likely to be injured. It is interesting to note also that the average age of our patients at the time of operation was 40 years. When the histories are analyzed further and it is noted that most of the patients have had intermittent symptoms for several years before the true cause of the disability was discovered, it will be seen that the protrusion occurred at an earlier age and at a time when a man probably is doing his most strenuous work and is most likely to sustain an injury.

The most common symptoms and signs and those which were of greatest value in arriving at a clinical diagnosis of protrusion of a lumbar disk were unilateral sciatic pain, which occurred in 78 per cent of cases, and bilateral sciatic pain, which was present in 16 per cent. In the other 6 per cent, backache alone or extension of pain elsewhere than along the course of the sciatic nerve occurred. Twenty-four per cent of the patients complained of pain which interfered with sleep at night. This is an important symptom when present. It is particularly suggestive of a lesion of a nerve root, but it is much more common in cases of intraspinal neoplasm than in cases of protruded disk. Another indication of involvement of a nerve root or of a radicular type of pain is accentuation of the pain on coughing, sneezing or straining at stool. Such accentuation occurred in 64 per cent of our cases. Paresthesias in the dermatome supplied by the compressed nerve root are of value in the diagnosis and localization of the protrusion. Paresthesias occurred in 50 per cent of our cases. On the other hand, sphincteric disturbance occurred in only 4 per cent. When such disturbance occurs, it usually means that a very large lesion is present and often a complete subarachnoid block, which is uncommonly associated with protruded disk.

The three neurologic signs which continue to be the most helpful in the diagnosis of protrusion of a lumbar disk are Lasegue's sign, positive in 84 per cent of cases, sciatic tenderness, present in 64 per cent, and diminution or absence of the achilles reflex on the side of the pain, noted in 60 per cent.

In only 25 per cent of cases was there any muscular weakness, sensory loss was detected in only 21 per cent. This is not difficult to understand in the light of the fact that the protrusion usually is small and compresses only one nerve root. Examination gave objectively negative results neurologically in 20 per cent of cases except for a positive Lasegue sign or sciatic tenderness or both. All patients suspected of having a protruded intervertebral disk should undergo a diagnostic lumbar puncture, so that the hydrodynamics of the spinal fluid may be

studied and a specimen of the fluid obtained for careful analysis. As has been stated, a protruded disk rarely produces subarachnoid block, particularly a disk in the lumbar region of the spinal column. The detection of such a block, therefore, would be suggestive of greater likelihood of an intraspinal neoplasm. The surgical treatment of such a condition requires essentially the same procedure, although in our hands the operation for the two conditions has been modified considerably. This subject will be dealt with under the heading "Surgical Technic for Protruded Intervertebral Disk."

The most important finding in the analysis of the spinal fluid in such cases is the total protein content of the spinal fluid. In the entire series, 40 per cent of the patients had less than 40 mg of total protein per hundred cubic centimeters of spinal fluid in the specimen submitted for analysis. This percentage of patients with normal or low values for total protein is higher than in the series of 300 cases previously reported. This can be explained, we believe, on the basis of a changed technic for diagnostic lumbar puncture. For about a year we have been puncturing the spinal canal at the interspace between the first and second lumbar vertebrae or between the second and third lumbar vertebrae, we obtain a specimen of spinal fluid for examination, and at the same time we replace the fluid in the caudal sac with air in order to obtain a spinogram or visualization of the lumbar canal. In this way we have been able to confirm the clinical diagnosis of protruded disk in a very high percentage of cases by means of one lumbar puncture, which obviates repeated punctures and shortens the examination considerably. However, since in most instances the lumbar protrusion occurs at the fourth or fifth lumbar interspace, we are puncturing the meninges and are obtaining our specimen of fluid at a greater distance from the lesion than when we tried in all cases to puncture as low in the spinal canal as possible.

ROENTGEN CONFIRMATION OF THE CLINICAL DIAGNOSIS OF PROTRUDED INTERVERTEBRAL DISK

In our earlier work on protruded disks, the diagnosis was confirmed prior to operation by roentgenoscopic and roentgenographic examination of the spinal subarachnoid space after injection of radiopaque oil.³ The accuracy of the detection or the exclusion of intraspinal lesions by means of this substance in the hands of the roentgenologists at the clinic was

3 Love, J. G. Protruded Intervertebral Disk (Fibrocartilage), *Proc Roy Soc Med* **32** 1697-1712 (Oct.) 1939

4 Love, J. G., and Camp, J. D. Root Pain Resulting from Intraspinal Protrusion of Intervertebral Disks. Diagnosis and Surgical Treatment, *J Bone & Joint Surg* **19** 776-804 (July) 1937

high, greater than 90 per cent. Because of the fact that radiopaque oil is absorbed slowly from the subarachnoid space, we dislike to use it in questionable cases, especially if the patients are not to have an operation. More recently, we have employed air in diagnosing lumbar protrusions. Air is a great addition to our diagnostic means because of its absorbability, but the observations made with it, according to Camp,⁵ do not compare favorably in accuracy with those made by means of radiopaque oil.

If a study in which air is used (spinogram) does not reveal the defect of a protruded intervertebral disk, it by no means excludes the possibility that such a lesion exists. Even roentgenoscopic examination of the spinal subarachnoid space after the introduction of iodized poppy-seed oil 40 per cent may fail to reveal a defect when a characteristic protrusion with its usual symptoms is present. This failure may be due to an anatomic abnormality of the cul-de-sac, such as congenital shortening, or it may be due to the fact that the protrusion lies too far laterally out in the foramen of exit of the spinal nerve. In 1 or 2 cases of our series it was impossible to explain the absence of a characteristic defect. When all findings point to the presence of a protruded disk and when the diagnosis cannot be confirmed roentgenologically, we feel that we are justified in advising an exploratory operation, for, in our experience, this can be done without the sacrifice of any bone and with a risk of less than 0.5 per cent, and the accuracy of our clinical diagnoses is extremely high. The following case history illustrates the point.

REPORT OF A CASE

A graduate nurse 25 years of age was suffering from intractable sciatic pain on the left side, which was aggravated by movement, coughing, sneezing and straining. Orthopedic examination by Dr. Meyerding revealed no cause of the severe pain. Neurologic examination gave entirely negative results except for tenderness along the course of the left sciatic nerve and inability to raise the leg, when held straight, more than 5 degrees from the horizontal. Air studies and spinograms gave negative results. Roentgenoscopic and roentgenographic examinations of the spinal canal disclosed no defect (fig. 2), and yet the pain of which the patient complained was so characteristically rootlike in type that we advised an exploration for a protruded disk. The patient had six lumbar vertebrae, the last one of which was fused with the sacrum. Since pain was on the left side, we knew that the lesion must be on the same side, and since with true sciatic projection of pain the protrusion is most likely to be at one of the last two interspaces, we exposed the ligamenta flava opposite the last two interspaces on the left. Immediately it was noted that the ligament between the fifth and sixth vertebrae was abnormally thick and fibrous. When it was resected, edema

⁵ Camp, J. D. The Roentgenologic Diagnosis of Intraspinal Protrusion of Intervertebral Disks by Means of Radiopaque Oil. *J. A. M. A.* **113**: 2024-2029 (Dec. 2) 1939.

of the nerve root, characteristic of a protrusion of the underlying disk was noted (fig 3) The fragmented and protruded portion of the disk (fig 4) was removed, with release of all pressure on the nerve root. Immediate relief of all pain

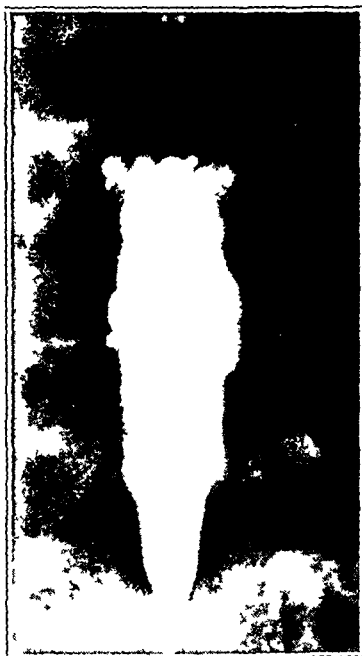


Fig 2—Anteroposterior roentgenogram showing a normal configuration of the caudal sac as outlined by radiopaque oil in a patient in whom a protruded fifth lumbar disk was found and removed

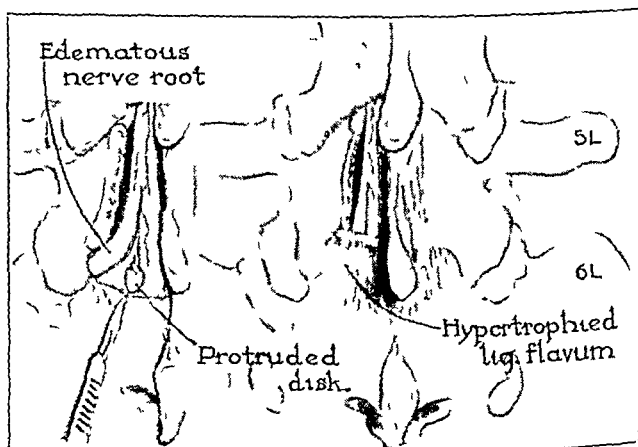


Fig 3—Drawing representing the protruded disk which was encountered at operation in spite of the negative findings on roentgenologic study with radiopaque oil illustrated in figure 2

occurred, and sedatives and narcotics, which had been required in large doses prior to operation, were no longer needed. The patient left the hospital on the twelfth day after the operation and returned to her nursing duties three months later.

SURGICAL TECHNIC FOR PROTRUDED INTERVERTEBRAL DISK

Every patient suffering from backache with or without "sciatica" is not a subject for intraspinal investigation, nor is such a one necessarily to be suspected of having a protruded intervertebral disk. Those who definitely need investigation to confirm or disprove the suspicion that a protruded intervertebral disk is the cause of their symptoms are the patients who have what in the past has been considered as intractable backache and "sciatica."

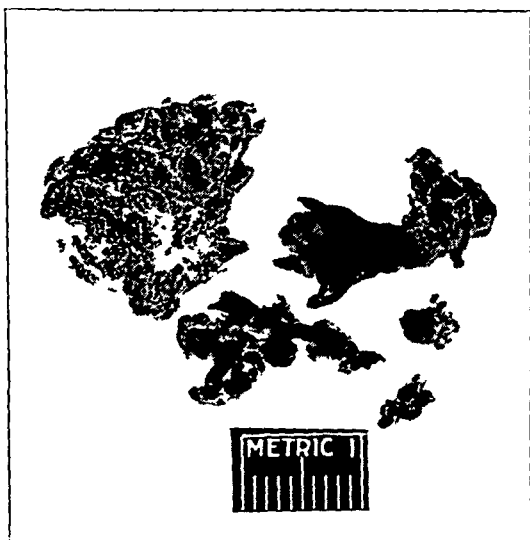


Fig 4—The darker structure represents the hypertrophied ligamentum flavum, the brighter pieces of tissue are the fragmented protruded portions of the intervertebral disk removed at the time of operation.

There are many pains in the back and legs which respond satisfactorily and often promptly to rest, either partial rest or complete rest in bed, others require physical therapy, with or without strapping or support to the back. The more severe conditions may be due to metabolic disturbances, tumors of peripheral nerves, intraspinal neoplasms or tumors of bone. Poisoning with alcohol or the heavy metals may also result in "neuritis" which for a time may be difficult to elucidate. In any case, a careful and thorough physical examination with roentgenograms of the spinal column and pelvis should be made.

When a diagnosis of protruded intervertebral disk is made and the surgical method of treatment is decided on, the operation should be performed by some one familiar with intraspinal surgery. The large

protrusions that produce partial or complete subarachnoid block are usually easily handled, but the smaller, more common protrusions are at times difficult to find even after they have been demonstrated roentgenographically, and hemorrhage from the extradural vessels may be extremely troublesome

The anesthetic agent of choice is ether administered by the open drop method. If there is any question regarding the patient's thorax or upper respiratory tract as far as recent infection or tuberculosis is concerned, we prefer to use pentothal sodium (sodium ethyl-1-methylbutylthiobarbiturate) intravenously or spinal analgesia. The patient is then placed on his side, instead of in the prone position which is usual for laminectomies. With pentothal sodium injected intravenously or with spinal analgesia, the excursions of the thorax are so slight that it would be unwise to have the patient lie thereon. Because pentothal sodium acts quickly, the patient should be on the operating table, prepared and draped for operation, before the venipuncture is made and before administration of the drug is begun. Suitable preliminary medication such as pentobarbital sodium, morphine sulfate and scopolamine hydrobromide in full hypnotic doses, given sufficiently early (before the patient is placed on the operating table) decreases the amount of pentothal sodium that is required. Some experience in administration of the drug is essential for smooth anesthesia.⁶ The only untoward effect of such anesthesia is a slight increase in bleeding from the muscles of the back. This is due to the well known vasodilating effect of pentothal sodium.

The operation may be done with the aid of paravertebral block, but in the majority of cases an anesthetic which blocks all sensory pathways in the lumbar region is to be desired. Most of the patients have had about all the pain they can stand, and they do not enjoy multiple insertions of a needle in the back, furthermore, when the involved nerve root is manipulated at the time of exposure of the protruded disk, considerable pain is produced even though the intradural portion of the nerve is bathed in procaine hydrochloride. Even under general anesthesia, it is not uncommon for the patient to move or tighten his muscles when the nerve is manipulated. Under general anesthesia, however, there is amnesia for this pain. In this connection we should like to record an interesting if unexplainable clinical observation. A few days after operation, gauze packs which have been placed along a nerve root at operation are removed. One of us (Love) has observed that earlier, when we used morphine sulfate in relatively large doses one half to three quarters of an hour before pulling the pack, the patient not only had excruciating pain while traction was being exerted on the gauze but was likely to

⁶ Adams, R. C. The Present Status of Intravenous Administration of Pentothal Sodium in Institutional and Private Practice, *Canad. M. A. J.* 38:330 337 (April) 1938.

complain of severe pain for a day or two thereafter. Since the introduction of pentothal sodium, used intravenously for this purpose, the patient not only is not conscious of the pain at the time of removal of the pack but does not have pain after he awakens, although he may have become tense when the pack was withdrawn.

Operative exposure of a protruded disk should be as accurate and as limited as possible, however, adequate room for the removal of all fragments is essential. The articular facets and pedicles should be preserved. No more bone should be removed than is absolutely essential for visualization and removal of the protruded portion of the involved disk. Whenever possible, a modified type of laminectomy should be employed, that is, instead of the removal of two or three pairs of laminae, the removal of a portion of one pair should suffice in most cases. During the past several months it has been the practice of one of us (Love) to perform what has been designated as "partial laminectomy", that is, no neural arch is interrupted. Instead, the margins of the laminae are removed. If there has been pain on one side only, the protrusion is typical and lateral and the ligamentum flavum is not markedly thickened on the opposite side, then, hemilaminectomy can be performed with satisfaction. At times, owing to great thickening of the ligamentum flavum and a listing of the patient away from the side of the protrusion, the lesion can be removed without the removal of any bone. It has been possible to remove the protruded disk in more than 20 cases without the removal of any bone from the spinal column. Theoretically, the less bone removed, the stronger the back will be postoperatively, and if at any subsequent time fusion should be required, it can be done with greater ease if none of the spinous processes or laminae has been removed.

For removal of a protruded intervertebral disk the patient is hospitalized the afternoon before operation. He is given a light supper, and before he goes to sleep, an enema of soap suds. If the patient is in severe pain, morphine sulfate or pentobarbital sodium is ordered, so that a good night's rest can be obtained. The next morning, all food and liquids are withheld and the patient is given hypodermically $\frac{1}{6}$ grain (0.01 Gm.) of morphine sulfate, on call to the operating floor he is given $\frac{1}{150}$ grain (0.00043 Gm.) of atropine sulfate. If the anesthetic is to be pentothal sodium, $1\frac{1}{2}$ or 3 grains (0.1 or 0.2 Gm.) of pentobarbital sodium is given on the evening before operation and is repeated on the morning of operation about one hour before the patient is called to the operating room. On call to the operating room, morphine sulfate and scopolamine hydrobromide are administered hypodermically. If ether is to be the anesthetic agent, morphine and atropine are the only drugs given on the morning of operation. During the period of induction nitrogen monoxide and oxygen are used, then ether is administered. When the patient is

asleep, an intratracheal tube may be inserted to facilitate easy, smooth respiration while the patient is lying prone with the neck turned to one side. The Magill intitracheal tube is particularly useful if the patient has a short thick neck.

After insertion of the intratracheal tube (this is done while the patient is still on a ward cart), the patient is placed on the operating table in the prone position. The torso is supported by the shoulders and pelvis, as this further facilitates breathing. Two large rolled pillows are placed longitudinally on the table so that the upper ends extend beyond the shoulders and rest under the clavicle. The lower ends of these pillows are crossed by a large flat soft pillow, which crosses the abdomen at the level of the iliac crests. The latter pillow, by adjustment, can be used to help flex the patient's back, a procedure which separates the spinous processes of the lumbar vertebrae and facilitates laminectomy. The skin is carefully shaved, not only that portion in the region of the contemplated incision but also the skin of the entire back which might be covered by the postoperative dressing and adhesive plaster. This is done not alone for aseptic reasons but also to avoid the discomfort attendant on removal of the dressings, particularly adhesive tape.

The skin is then thoroughly washed with ether and then with alcohol. Afterward, two coats of tincture of merthiolate are applied. The merthiolate should be used generously and widely. It is our feeling that wide application is good, for during any surgical procedure, particularly in warm weather, perspiration is likely to soak through the sterile drapes. If a generous application of antiseptic is on the skin, there is less likelihood of contamination of the wound.

When the drapes are placed they should not be more than $1\frac{1}{2}$ inches (3.8 cm) to either side of the spinous processes, and only sufficient skin to accommodate the length of the proposed incision should be exposed. The incision is made straight in the midline extending across the tips of two spinous processes. The muscles (*erectores spinae*) are reflected from the bone (spinous processes and laminae) subperiosteally (fig 5c). This minimizes bleeding and trauma to the muscles and facilitates closure. If the operation is to be a hemilaminectomy, the muscles need to be reflected only on one side, however, if the wound is short, the self-retaining retractors work best if all of the prongs are at an equal depth in the wound, and then it often is advantageous to view the other side of the ligamentum flavum, which may be hypertrophied and may therefore require resection.

It is not necessary to strip the muscles widely or to undercut or crosscut them. The packing of gauze sponges between the bone and the reflected muscles not only controls small bleeders but also irons out the muscles, so to speak, and when the self-retaining retractor is inserted

it often is surprising to see the large amount of exposure obtained. While the gauze is packed in the depths of the wound, the cutaneous and subcutaneous bleeders which have been caught with points are electrocoagulated. It is nearly impossible to ligate these bleeders, and catgut knots are not well absorbed when placed superficially in the back. When the superficial bleeding has been controlled, the gauze sponges are removed from the depths of the wound and the Adson self-retaining laminectomy retractor (fig 5 *d*) is placed so as to hold the muscles away from the spinous processes and midportions of the laminae. If a bilateral or partial laminectomy is to be done, the tips of the spinous processes are sheared off with a cutting forceps (fig 5 *f*). If the operation is to be a hemilaminectomy, none of the spinous processes is

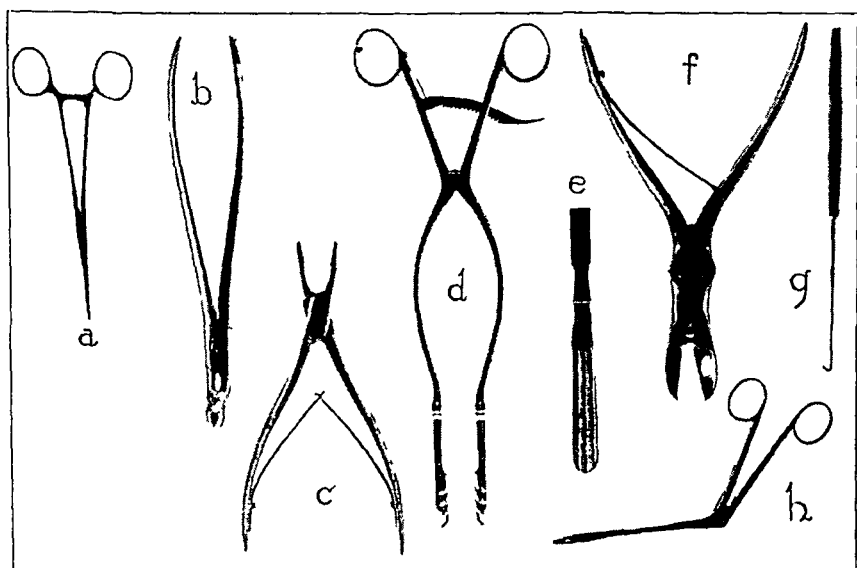


Fig 5—Special instruments used in the removal of a protruded intervertebral disk. *a*, Ochsner's 6¼ inch (156 cm) mortis joint forceps, *b*, Adson's curved gouging rongeur, *c*, Adson's laminectomy straight rongeur, *d*, Adson's laminectomy retractor, *e*, Adson's laminectomy chisel, *f*, double action Liston cutting forceps, *g*, Love's nerve retractor, and *h*, Grunwald nasal ethmoid forceps.

removed. At most, two spinous processes are sacrificed. The portions of laminae to be sacrificed are removed with a heavy duty bone-biting forceps or rongeur (fig 5 *b*). In a hemilaminectomy the lamina can be removed best with a straight single-acting rongeur (fig 5 *c*), as large instruments cannot be inserted between laminae. The bone should be removed from around the ligamentum flavum so that the size, color, resistance and thickness of the ligament can be noted.

We feel confident that in the past many abnormal ligaments have been removed with rongeurs without their abnormality having been

noted When the ligament is dissected free, it should be grasped with a forceps (fig 5 *a*) and then be resected as widely as possible in order to remove any of the usually thickened ligament which might compress the nerve root posteriorly By this time, the enlarged, edematous, discolored and displaced nerve root should have been visualized The involved nerve is frequently several times larger than normal, is reddish to purplish and is displaced posteriorly and laterally or at times mesially Retraction of the nerve root will reveal the characteristic posteriorly protruded fibrocartilaginous mass or protruded disk The protruded portion should be removed extradurally, and even if the dura mater is to be opened for the removal of radiopaque oil, this should be postponed until the protruded portion of the disk has been removed There are three good reasons for this first, there is less bleeding, and it is more easily controlled if it occurs, second, there is less likelihood of trauma to the already injured nerve root if the cerebrospinal fluid is within the dural sac acting as a buffer and, third, if one should accidentally open an inflammatory mass such as tuberculous abscess, the meninges would not be contaminated Pus on the outside of the dura mater is relatively innocuous whereas pus in the subarachnoid space is likely to result in meningitis and death

Many of the protruded bodies consist of completely fragmented fibrocartilage which has ruptured through the posterior longitudinal ligament, as soon as the involved nerve root is retracted (fig 5 *g*) the fragments need only to be picked from the wound Others are still held partly in check by the posterior longitudinal ligament, and this must be opened before the fragments can be removed At times the ligament is so thin that the bayonet forceps can easily be pushed through the dome of the mass, and then the protruded body is removed At other times incision of the portion of ligament that overlies the protruded disk is necessary A ureteral knife serves this purpose well Occasionally the protruded body is calcified or ossified, and then it is necessary to use a curet or rongeur for its removal

Rarely is it necessary to proceed transdurally in order to remove a protruded disk Some midline protrusions, which are relatively infrequent, particularly those which have produced a block and paraplegia, are so large and have caused so much edema and enlargement of the cauda equina on both sides of the spinal canal that they are best removed transdurally The dura mater is incised posteriorly over the site of the protrusion, the cerebrospinal fluid is allowed to escape, and then the spinal canal proximal and distal to the protruded mass is packed off with cottonoid strips This is done in case there is bleeding when the dura mater is incised anteriorly The dura mater over the dome of the pro

trusion is then incised. Again the protrusion may have ruptured through the posterior longitudinal ligament, or it may be necessary to incise this ligament before the protruded disk can be removed. It is essential that all fragmented cartilage be removed. The use of a nasal forceps (fig 5 h) facilitates the removal of small fragments that otherwise might be overlooked. It is not necessary to suture the dura mater anteriorly, but the posterior incision should be closed with a continuous suture of fine silk.

If radiopaque oil has been used in confirming the diagnosis of a protruded disk prior to operation, the radiopaque oil should be removed from the subarachnoid space before the wound is closed. If the protruded body has been removed extradurally, the dura mater and arachnoid should be opened with a ureteral knife for a distance of 1 cm and the oil removed. While the operation is being performed, the patient's head and shoulders should be elevated, by lifting the head of the operating table, so that the oil will be collected in one mass at or near the site of the protrusion. The oil is best removed by means of a suction apparatus which is standard equipment in all neurosurgical amphitheatres. Care should be taken lest one or more roots of the cauda equina be caught by the sucker tip. This would result in unnecessary trauma and possibly in residual disability. At times, removal of the oil may be facilitated by irrigating the subarachnoid space proximal and distal to the most dependent point, where the oil tends to accumulate, with physiologic solution of sodium chloride at a temperature of 100 F (37.7 C). The saline solution is injected through a no. 10 French urethral catheter by means of a bulb syringe. Whenever possible, the operative wound should be closed without drainage. The muscles (*erectores spinae*) are sutured together across the midline with interrupted sutures of no. 1 chromic single-stranded catgut. The fascia is sutured in a similar fashion. The edges of skin are then approximated with a continuous silk or dermal suture. Occasionally a better closure is obtained if catgut is used to suture the subcutaneous layer, particularly if a long incision has been employed.

At times bleeding from the extradural vessels, particularly from the veins, is troublesome and some special means is necessary for its control. All laminectomy wounds should be dry before they are closed, lest a postoperative hematoma form and result in serious complications, such as paralysis. Often the simple expedient of placing a cottonoid strip on the extradural vessel and applying suction is sufficient to control the bleeding. At times a small pledget of muscle obtained from the *erector spinae* and applied to the bleeder suffices. At other times bleeding cannot be controlled by any of these methods. The vessel may then be

sought after and one or more silver clips applied to obliterate its channel. These vessels are often elusive, and considerable time may be lost while hunting for the bleeding point. Coagulation of the bleeder with the electrosurgical unit is employed by some, but this method may result in injury to nearby nerve roots. The current may "jump" to a nerve root, and this may not only injure the nerve root but also it is likely to make the patient move because of stimulation of the muscle or muscles supplied by the irritated nerve root, this often increases the bleeding and obscures the surgical field. In our experience the most satisfactory way to control extradural bleeding is with plain gauze 1 inch (2.5 cm) wide. The gauze is packed extradurally against the bleeding vessel and then suction is applied to a wet cottonoid strip placed over the gauze. In a short time all bleeding ceases, then the cottonoid strip is removed, and the muscles are closed around the gauze strip. Such a gauze strip should not be disturbed for forty-eight to seventy-two hours.

After the operation but before the surgical drapes are disturbed, the skin near the incision should be washed with saline solution, and then a small gauze dressing moistened with alcohol should be applied over the line of suture, this dressing should be covered with a sterile soft absorbent (cotton) pad. The drapes are removed, and then the dressings are securely fixed in place with strips of adhesive tape. The tape should seal the upper and lower ends of the dressings to the skin, but the lower strip of tape should be kept as far away from the natal cleft as possible, to avoid contamination. The center and sides of the dressings, we feel, are best left unsealed. This permits air to get to the wound and allows evaporation of perspiration that forms under the dressing. If the cutaneous edges remain moist, they may macerate, and this would facilitate the development of infection.

POSTOPERATIVE CARE

The treatment of a patient following the removal of a protruded intervertebral disk is important, and we believe that it plays an important role in the restoration of the patient to an active useful life within a time that is consistent with good surgical judgment and well within the limits of the time required for convalescence from any major surgical procedure.

The patient is taken from the operating table to his room on a surgical cart. Care should be exercised to prevent chilling of the patient while he is wheeled along the corridors or transported to another floor by elevator. The bed to receive the patient should have been prepared and warmed. Boards are placed under the mattress to prevent sagging of the mattress and consequently of the patient's back. The patient is

placed in bed on his side, and pillows are placed against his back to prevent him from rolling backward onto his wound. A competent nurse should be constantly in attendance until the patient is fully awake and able to cooperate. Special nursing care is not required after the patient has regained consciousness.

When the patient becomes conscious and begins to complain of pain in the back at the site of the operation, he is given morphine sulfate hypodermically to control the pain. This should be repeated as often as every four hours for the first two or three days, if necessary. By this time, it is usually unnecessary to use any analgesic stronger than acetylsalicylic acid in doses of 5 grains (0.3 Gm.) each. It should be emphasized that no sedative should be given postoperatively until the patient is awake and is able to move his toes on command. It is essential that the patient's ability to move his toes and to recognize touch and pain in his extremities be checked frequently during the first few days following operation. If any diminution of this ability occurs, postoperative bleeding should be suspected, and the wound should be opened without delay. If hemorrhage has occurred, its prompt recognition coupled with removal of the hematoma should prevent the persistence of weakness or anesthesia. If a postoperative hemorrhage is not recognized, permanent damage may result from compression of the spinal cord or cauda equina.

During the first forty-eight hours the patient is turned every four hours by a group of nurses, but he is not allowed to lie on his back. Pressure against the wound is avoided until it is healed (about ten days). After forty-eight hours the patient is allowed to turn himself as often as he desires. To lie on one's side for four hours results in rather severe distress in the hips. This is largely avoided by permitting the patient to be turned when he becomes uncomfortable; in addition, the amount of sedatives required is kept at a minimum by such treatment. The patient's morale is improved when he realizes how much he can do alone. Avoidance of morphine is to be desired. The patients are allowed fluids after nausea has ceased and solid food as soon as desired, usually the next day. On the morning of the third day a simple soap suds enema is usually given. Care should be taken to avoid contamination of the dressing at the time of evacuation of the bowel particularly if the operation was for lumbosacral protrusion in which the dressing of necessity is placed low on the back and near the nates. If the dressing should accidentally be soiled, it should be changed immediately and the wound should be painted with an antiseptic solution to avoid contamination.

The patient from whom a protruded disk has been removed without the removal of any bone is allowed to stand beside the bed or go to the bathroom the day following operation if unable to void lying in bed.

Those who have suffered interruption of continuity of a neural arch ordinarily are catheterized after operation and every eight hours thereafter. If unable to void after three days of intermittent catheterization, an inlying urethral catheter is employed for continuous drainage until the patient is up and around, usually the tenth to twelfth day. The cutaneous sutures are removed on the tenth postoperative day, and the patient usually leaves the hospital by the twelfth day.

PROTRUDED INTERVERTEBRAL DISK AND FUSION

A few years ago patients who were being treated for protruded intervertebral disks were having bone grafting or fusion operations performed. Today such operations are comparatively infrequent. Naturally, the question arises as to whether or not fusion should be performed at the time of removal of the protruded disk.

There are certain definite indications for fusion on which orthopedic surgeons are agreed, there are conditions in which fusion is open to question, and there are conditions in which it is definitely contraindicated. It is our feeling that the patient should be considered individually and that treatment should be adapted to the particular indications which are presented in his case.

The patient who has a protruded disk and well developed spondylolisthesis should have fusion performed at the time of removal of the protruded disk. The patient who has associated spondylolysis probably should have fusion done at the time of surgical removal of the protruded disk. The patient who has extensive lumbosacral arthritis and a static type of backache in addition to a protruded disk and its resultant symptoms probably should have fusion done at the time when the protruded disk is removed.

However, fusion will not be found necessary or indicated in a high percentage of cases. The orthopedic surgeons of the clinic, Henderson, Meyerding, Ghormley and Macey, who see with us in the neurologic and neurosurgical departments every patient suspected of having a protruded disk, have found it necessary to fuse the spinal column in only 15 of more than 500 operations for protruded intervertebral disk.

Fusion not only is not indicated but is definitely contraindicated in many such cases. For the young person who has not reached maturity and whose bones are still growing, bone grafting of the spine is not ordinarily undertaken. We have removed protruded disks from several patients who were in their middle teens. For those of advanced years, fusion or any other surgical procedure which would require a prolonged period of immobilization in bed is contraindicated. We have successfully removed protruded disks from many who were in their late sixties.

and early sevenies. These patients usually have been allowed to get out of bed five or six days after operation in order to avoid pulmonary complications, this, of course, could not be allowed if fusion were performed.

EVOLUTION OF THE TECHNIC FOR REMOVAL OF PROTRUDED INTERVERTEBRAL DISK

Earlier in our experience with the surgical treatment of protruded intervertebral disk a comparatively extensive and time-consuming operation was performed. It seemed necessary to have a wide exposure of the involved nerve root and protruded disk. Usually two and often even three pairs of laminae were resected (fig 6) a procedure which is commonly employed for the removal of intraspinal neoplasms. From the first, however, we have maintained that the articular facets should be preserved. As our experience with this lesion increased we found that the sacrifice of one pair of laminae sufficed to expose the involved nerve root and the underlying protruded body (fig 7). We then modified the operation and performed a hemilaminectomy of one vertebra in cases of unilateral protrusion with unilateral symptoms (fig 8). This operation was then modified and became what we call a partial laminectomy, namely removal of only the margins of the laminae without interruption of a single neural arch (fig 9). On Dec 1 1938, while we were carrying out an operation planned as a hemilaminectomy for a patient who had comparatively marked scoliosis toward the side opposite the lesion, we found that the protruded portion of the disk could be removed without the removal of any bone (fig 10). No portion of the neural arch or spinous process was sacrificed. By resecting the hypertrophied ligamentum flavum—such hypertrophy is an almost constant accompaniment of protruded disk—adequate exposure for removal of the fragment cartilage was obtained. After such an operation the roentgenograms of the spinal column appear exactly the same as those made prior to operation. In the illustration a silver clip placed in the center of the disk at the time of removal of the protruded part of the disk indicates the site of removal and confirms the statement that the spinal canal was entered without the removal of any bone (fig 11). Such an operation requires a very short incision (fig 12), a minimum of trauma to the muscles and a short period of anesthesia and permits the patient to be up and around in a much shorter time than otherwise would be necessary. The shortening of the period in the hospital is a boon to the patient's morale and minimizes the economic strain that

7 Love, J. G. Protruded Intervertebral Disks with a Note Regarding Hypertrophy of Ligamenta Flava, *J. A. M. A.* 113:2029-2034 (Dec. 2) 1939.

hospitalization entails in the majority of cases. Patients who have no bone removed can be allowed out of bed the day after operation a distinct advantage particularly for elderly and obese patients.

In a small percentage of cases a fusion operation is indicated at the time of removal of the protruded disk. Preservation of all laminae and

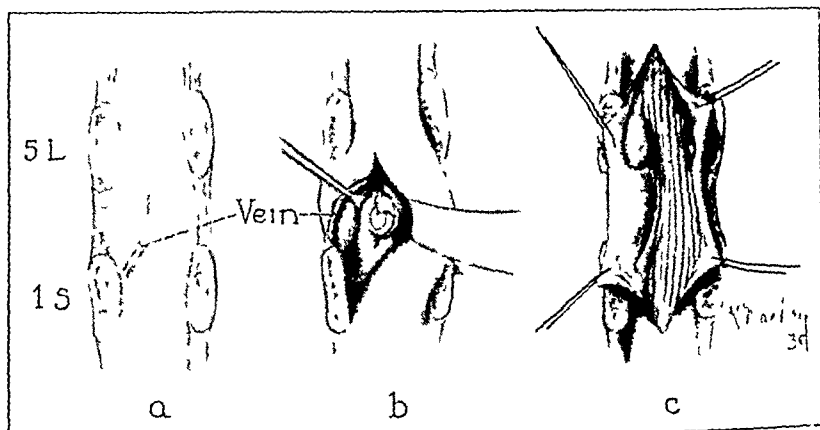


Fig 6—Drawing representing certain steps in the course of a classic laminectomy in which two spinous processes and two pairs of laminae have been sacrificed to expose a protruded intervertebral disk.

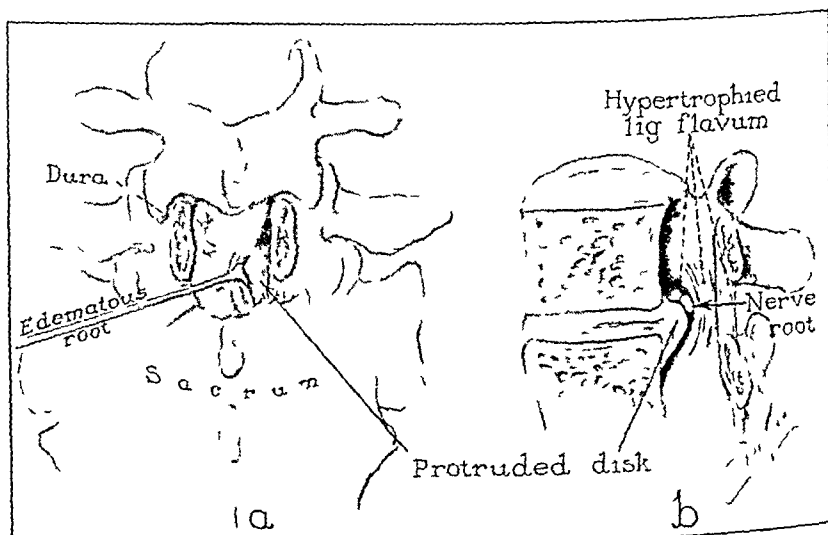


Fig 7—Drawing representing exposure of a protruded intervertebral disk by removal of one spinous process and one pair of laminae.

spinous processes gives the orthopedic surgeon a much better and broader field for anchoring of the bone graft. This is particularly desirable in cases of spondylolisthesis,⁸ for which a double bone graft is advisable.

⁸ Meyerding, H. W. Spondylolisthesis as an Etiologic Factor in Backache. *J. A. M. A.* 111:1971-1976 (Nov. 26) 1938.

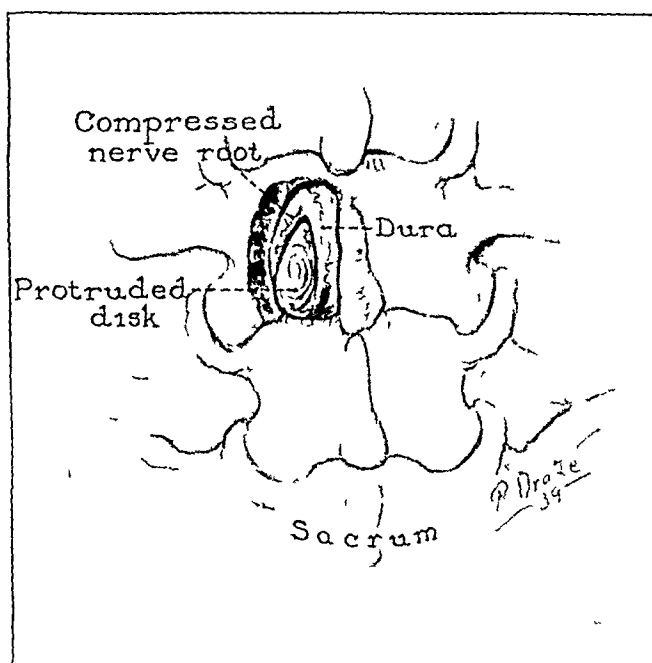


Fig 8—Drawing of a protruded intervertebral disk exposed by hemilaminectomy. The spinous process and the lamina of the opposite side are preserved.

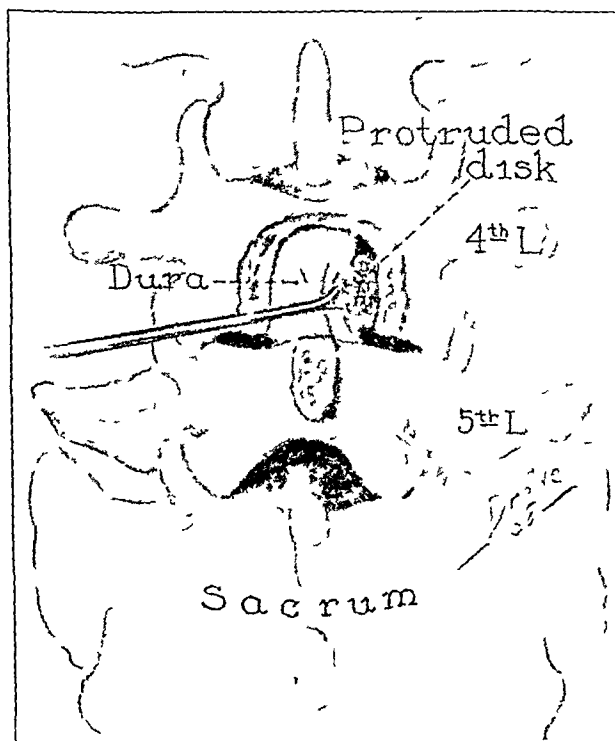


Fig 9—Drawing of a protruded intervertebral disk exposed by partial laminectomy, a procedure in which no neural arch is completely interrupted.

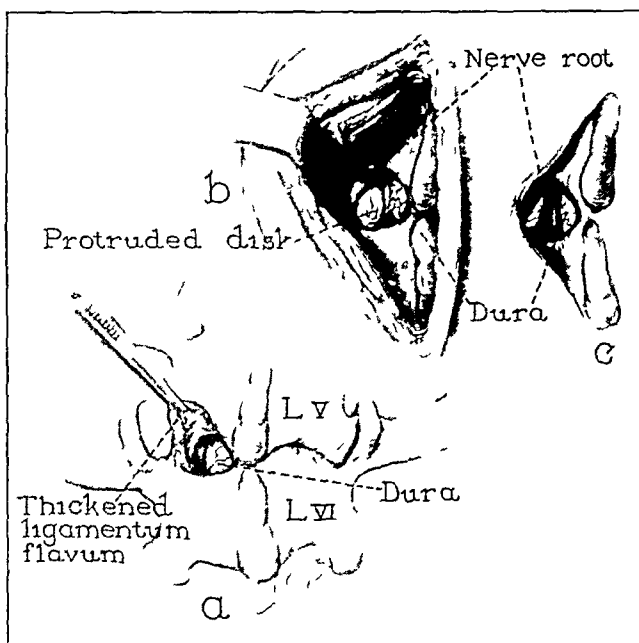


Fig 10—Drawing showing the removal of a protruded intervertebral disk without laminectomy and without removal of any bone *a*, resection of the hypertrophied ligamentum flavum, *b*, exposure of the protruded portion of the disk, and *c*, restoration of the spinal canal to normal size and shape after the protruded part of the disk has been removed



Fig 11—Anteroposterior roentgenogram showing evidence of a hemostatic silver clip in the center of the lumbosacral disk from which a protruded body was removed without removal of any bone

RECURRENCE OF PROTRUDED INTERVERTEBRAL DISK

When a protruded intervertebral disk has been removed, does further fragmentation and protrusion of that disk occur? This question has been asked many times. When we first began to remove protruded intervertebral disks in large numbers we asked ourselves that same question. That further protrusion would occur, particularly if the patient subjected his back to unusual stress or strain, seemed likely since the entire disk is never removed. Only those parts of the disk that are fragmented and lying more or less free from the main bulk of the disk are removed at



Fig. 12—Photograph of patient two weeks after operative removal of a protruded disk, to show the small incision which is required

operation. Nature is kind to human beings, and she is most beneficent to those who wield the scalpel. If she were not, most operations on the colon would be fatal, patients having tonsillectomy would bleed to death, and all patients subjected to operative removal of intervertebral disks would return with recurrent symptoms. If nature is given a chance, she will heal over the raw surfaces left by the surgeon and the resultant healed wound often will be stronger than the original tissue, the continuity of which was severed by the surgeon.

To be sure, the surgeon should do his utmost to leave nature unhandicapped in her endeavor, and he should warn his patients of the pitfalls into which they may stumble. The patient who has had a protruded disk

removed should be specifically instructed as to what he must not do until sufficient time has elapsed for firm healing to have taken place. It is our practice at the time of dismissal of such patients to advise them to do no lifting or straining for a period of three months from the date of dismissal. They are advised not to carry their luggage, move furniture about the house or lift children or any object likely to put stress on the back. They are told not to dance or play golf. Clerks and those employed in sedentary occupations are advised not to return to work for three months. It has been found that even a swivel chair becomes uncomfortable when occupied for six to eight hours by a patient recently operated on. If the patient returns to work too soon, he is likely to have vague aches and pains, and soon he indulges in self pity, which is accentuated by overzealous friends and anxious relatives. In time he may even assume that he has obtained no relief from his operation and that his condition is just as poor as, or even worse than, it was before the operation.

It is particularly important to warn day laborers, truck drivers and others who are accustomed to hard manual work to return to their former duties gradually. Such persons must regain confidence in their ability to carry on. This is especially true if compensation or insurance is involved. If the patient has gone for a long time without the true nature of his disability being recognized, and if he has been considered by some to have a post-traumatic neurosis or even to be a malingerer, he should be given special consideration and reassurance until he has been reeducated and shown that he can carry on in a normal way.

In spite of our best efforts and the giving of sound advice based on our knowledge of anatomy, physiology, pathology and psychology and our considered clinical judgment, some patients will claim that they have not been benefited by treatment. Others will state that they were better or even completely relieved for a time but that, without any violation of professional advice, the symptoms returned. A few will return years afterward and relate a history of having been completely free of pain following operation until on a particular day when unusual stress or strain was applied to the back. For instance, this incident might have been followed by backache which rapidly developed into all the symptoms for relief of which the original operation had been performed, or at the time of straining of the back all symptoms might promptly have returned. Of course, there is no reason why another intervertebral disk could not protrude, and this is particularly true in the light of our relatively high incidence (approximately 10 per cent) of multiple protrusions found at the time of the original operation. However, our experience leads us to conclude that if there is a recurrence of symptoms due to a protruded

intervertebral disk, it is most likely due to further protrusion at the site of the original protrusion. In more than 500 operations for protruded intervertebral disks, we have encountered only 5 recurrences, in all 5 of which the disk which was the site of a protrusion at the time of the original operation was again involved.

The first case of recurrence was reported in the *Proceedings of the Staff Meetings of the Mayo Clinic*.⁹ Relief was obtained following the removal of a large protruded portion of the fourth lumbar disk. However, two months after the patient's return home he began to have a recurrence of his old symptoms, following a head cold. Whether or not he had bronchitis and cough is not known. Shortly thereafter, the sciatic pain became markedly exaggerated while he was carrying some pails of water. He was operated on a second time seven months after the original laminectomy, and a large amount of protruded fibrocartilage which came from the fourth lumbar disk was removed, with relief of his symptoms. After that experience, more care was taken in searching for additional fragments of the disk, particularly fragments still remaining within the center of the disk. It seemed desirable not to curet the disk and cartilaginous plates attached to the vertebral bodies or to use a strong bone-cutting instrument within the disk. In looking around for a suitable instrument to pick up fragments from the space between the vertebral bodies, one of us (Love) discovered that the rhinologist's nasal punch was admirably suited for this work (fig 5*h*). Often, after all fragments seem to be removed, this instrument will enable the operator to bring out one or more additional free fragments from within the disk. Naturally, if these fragments are not removed, a recurrence can be expected.

The second case of recurrence was that of a man who had had a protruded fragment of the fourth lumbar disk removed Feb 7, 1938, it had caused intractable left sciatic pain, which had confined him to bed and had resulted in great loss of weight. Removal of the protruded portion had afforded immediate and complete relief. In May 1939, while fishing, he turned around in a boat to pick up a minnow bucket and was suddenly seized with pain low in the back and along the distribution of the left sciatic nerve. The pain was so severe that he was returned to our care on a stretcher. Roentgenoscopic examination of the spinal canal after injection of radiopaque oil revealed evidence of partial obstruction, the shadows were not characteristic of any particular lesion, that is, it could not be stated whether stoppage of the oil was the result of adhesions at the site of the old laminectomy or of a space-occupying lesion such as protrusion of the disk. In view of the nature of the symptoms and the characteristic root type of pain, operation was advised. On Aug 17, 1939, a large protruded fragment of the fourth lumbar disk was removed, with complete relief of symptoms.

The third case of recurrence was that of a man 47 years of age. He first registered at the clinic on March 24, 1937, when he was 45 years of age. At that time he complained of intermittent backache and left sciatic pain of five years' duration. The patient's symptoms had started in the winter of 1931-1932, when he had first noted left sciatic pain which could not be attributed to any specific cause. In January 1937 the pain became more severe, and from then on

⁹ Love, J. G. Recurrent Protrusion of an Intervertebral Disk, *Proc Staff Meet, Mayo Clin* 13 404-408 (June 29) 1938.

he was unable to work until after treatment at the clinic. Usually there was considerable aggravation of the pain around 4 a. m. The backache was aggravated by standing up and by riding in a car.

Examination showed a listing of the patient toward the left, and all spinal motions were limited. There was tenderness over the lumbosacral area. The right leg was about 3 inches (7.5 cm.) shorter than the left, owing to an old fracture of the tibia. This was compensated for by use of a higher heel on the right shoe. Neurologic examination revealed that both achilles reflexes were normal. Examination of the spinal fluid revealed a total protein content of 50 mg. per hundred cubic centimeters.

A clinical diagnosis of protruded intervertebral disk was made, and a study was performed with radiopaque oil. Examination by Dr. Camp revealed a defect typical of protruded intervertebral disk at the fourth lumbar interspace. Laminectomy was performed, and a midline protrusion of the fourth lumbar disk was removed. The laminectomy consisted of removal of the spines and laminae of the third and fourth lumbar vertebrae and part of those of the fifth. Extradural exploration revealed no evidence of protruded intervertebral disk. The dura was incised, and much edema and matting together of the roots of the cauda equina over the fourth intervertebral space were detected. The roots were separated, and there was a classic midline protrusion of the fourth lumbar intervertebral disk. Incision of the dura mater permitted escape of a large fragment of cartilage, following which the canal was normal in size and shape. Because of slight oozing, a muscle pledget was placed in the dural incision for hemostatic purposes. The dura was closed with continuous sutures of silk. A piece of folded membrane was placed over the line of suture. The wound was closed in the usual manner, and one Penrose drain was used.

The patient was kept in bed for thirteen days following operation. His convalescence was uneventful, and at the time of dismissal he was completely relieved of pain. Postoperative neurologic examination gave negative results.

The patient returned Aug. 16, 1939. He stated that he had been well, had experienced no pain and had walked without aid and without abnormality, following his operation, until July 31. On that day he turned to his left and leaned over toward the floor to pick up a package. Before he could pick it up he was seized with a sudden severe pain which started in the left buttock and followed the distribution of the sciatic nerve downward to the heel. Since that time the pain had been severe and constant. At times the left leg became numb, but there had been no noticeable change in its strength. There were no symptoms referable to the right leg. He stated that whereas prior to his first operation the pain was more severe in the back than in the leg, since the recurrence of pain in July all the pain had been in the leg and there was no pain in the back. Conservative treatment had been tried at home without relief.

Examination by Dr. Ghormley revealed obliteration of the lumbar lordosis with a list to the right. All spinal motions were limited 50 per cent. Neurologic examination revealed slight diminution of the left achilles reflex. The Kernig and Lasague signs were present. A diagnostic spinal puncture and a spinogram made at the same time on August 17 revealed no air below the fourth lumbar interspace. The total protein content was 45 mg. and there was 1 lymphocyte. It was advised that the old site of laminectomy be explored in association with Dr. Ghormley, who felt that in view of the recurrence of symptoms a bone graft should be performed.

On August 21 we opened the old wound, dissected the scar tissue away and palpating opposite the fourth interspace found a mass. At first we could not be certain whether this represented scarring or recurrent protrusion of the disk. When the nerve root was retracted, there was classic evidence of protrusion of the disk, and when the posterior longitudinal ligament, or whatever had developed to take its place, was incised, a huge fragment of cartilage was removed, this was one of the largest that we have ever seen. When this was removed, there was a large cavity between the vertebrae. After the disk had been removed, a graft, which had been taken from the left tibia and divided into two pieces, was placed by Dr. Ghormley from the third lumbar to the second sacral vertebra.

The fourth case of recurrence was that of a woman 39 years of age, who had right sciatic pain. On March 15, 1937, laminectomy was performed with removal of a protruded portion of the fourth lumbar disk by resection of the spines and laminae of the fourth and fifth lumbar vertebrae. The patient returned in June 1939 and stated that following the operation in 1937 she had not had further backache or sciatica until February 1939, when she began to have mild aching pain in the right buttock and lower lumbar region. Six weeks prior to this admission there was a sudden onset of pain low in the back with extension of the pain to the right thigh and external surface of the right leg. The pain was worse on coughing and sneezing, but there was no pain at night.

The results of examination were negative. The achilles reflexes were normal. There was no Kernig sign, and there was no sensory disturbance to be detected objectively, however, the patient complained of paresthesias over the lateral aspect of the right thigh and leg. The patient was seen in consultation by Dr. Meyerding, who advised that a corset be used for support and that physical therapy be employed over the lower part of the back. We told the patient and her husband that if the symptoms did not subside further surgical work would have to be considered. She returned after a thorough trial of physical therapy, which included hot baths, and stated that instead of her condition becoming improved, it had become worse.

On August 22 the old wound was opened, and underneath the nerve root on the right side was a classic example of recurrent protrusion of the fourth lumbar disk. One huge fragment and several smaller fragments were removed, after which there was no pressure on the cauda equina. Dr. Meyerding then proceeded with a bone graft. An osteoperiosteal graft 2 inches (5 cm.) long and 1 inch (2.5 cm.) wide, taken from the left tibia, was sutured over the exposed dura and the outer layer of the periosteum toward the dura mater, and multiple bone chips were placed along the course of the graft. A double bone graft taken from the left tibia was sutured so as to bridge the third, fourth and fifth lumbar vertebrae and upper two segments of the sacrum. Cancellous bone removed by use of a curet was picked around it. Arthrodesis of the facets of the third and fourth lumbar vertebrae was performed on both sides.

The fifth recurrent protrusion was encountered in a man 29 years of age. On June 17, 1937, transdural removal of a large portion of a lumbosacral disk which protruded in the midline was effected. Prior to this the patient had had backache and "sciatica" intermittently for eight years. After operation he was completely relieved until Sept. 19, 1939, when, after heavy lifting he noted that a sudden sneeze gave rise to pain in the lower part of the back. The pain gradually became worse and within five days extended down along the course of the sciatic nerve. On October 4 another large protruded portion of the lumbosacral disk was removed extradurally, and then a graft was taken from the tibia and applied to the spine. It extended from the third lumbar to the second sacral spinous process. The latter procedure was performed by Dr. Ghormley.

If a recurrence is encountered, how should it be handled? Should it be treated as if it were the original lesion, or is there anything which one can do to prevent further recurrences? This cannot be answered dogmatically and without reservation. We believe that each case should be considered as an individual problem and that the final conclusion about the matter should be reached only after all factors have been considered, such as the presence or absence of congenital anomalies of the back, the extent of the original laminectomy, the degree of relief following the first operation, whether or not there was some residual static backache, the type of work to be done by the patient, his build, his age, his general condition and the cause of the recurrence, if any. Doubtless, in some of the cases in which a recurrence occurs fusion will be required, in others an excellent result will be obtained from removal of the protruded portion of the disc without fusion. We cannot, of course, be certain that a spinal bone graft or fusion will prevent further trouble. Certainly, if the patient has a well back internal fixation in the form of a bone graft is desirable.

Of the 5 cases of recurrent protrusion which we have encountered, in 3 fusion (a bone graft obtained from the tibia and applied to the back) was performed at the same time that the recurrent protruded body was removed. In the other 2 cases simple removal of the protruded fibrocartilage gave relief. It is too early yet to know the answer regarding recurrent protrusion, even in these 5 cases, for, at the time of this writing, 1 of the patients is still in the hospital.

RESULTS OF OPERATIVE REMOVAL OF PROTRUDED DISKS

In medicine and surgery it has become customary to report results as based on "five year cures," and we believe that this is a fine thing. It tends to avoid undue enthusiasm for any so-called new type of therapy. Since most of our patients have been operated on within the last five years, it is too early to know what the ultimate results will be. This is particularly true in evaluating results in groups of patients whose illness is characterized by remissions.

To date we are gratified with the results which we have obtained in this large group of 500 patients, most of whom had suffered for many years from intractable backache and sciatic pain. Craig and Walsh¹⁰ in reporting on "the present status of the protruded disk syndrome" before the International Congress of Neurology held in Copenhagen, Denmark, in August 1939, made the following statement: "Following any operative procedure the amount of relief obtained depends upon certain factors, among which are the accuracy of diagnosis, the operative procedure, the postoperative care, the duration and severity of the pain,

10 Craig, W. McK., and Walsh, M. N. Unpublished data.

the patient's susceptibility to pain, medicolegal questions, settlement of compensation and last, and very important, the patient's reaction to his disability"

When we come to analyze our data on the basis of five year cures, we shall find it, therefore, an extremely difficult problem, for today, unfortunately, the questions of liability, compensation and insurance loom large on the horizon and add complications compounded to an already knotty problem. There have been only two hospital deaths in our entire series of cases in which operation was performed. One death was reported in *The Journal of the American Medical Association*¹¹. The subsequent death was due to bilateral suppurative parotitis, which became fulminating and extended to involve the mediastinum as mediastinitis. The patient's wound was already healed, and he had been relieved of the severe sciatic pain for which the operation was performed.

A short resume of a case will serve to illustrate how disabling protrusion of a disk can be, what the usual symptoms and signs are and what can be expected after surgical removal of the protruded body.

A patient 17 years of age was well until two months prior to operation when, while swimming, she experienced pain low in the back. The next day she was unable to straighten up. Within a few days mild paresthesias occurred on walking. At times there was radiation of pain down the posterior aspect of both thighs to the knees and occasionally to the right ankle and instep. The pain was exaggerated by spinal motion, attempts at straightening the back, laughing and coughing. Pain at night occasionally disturbed her sleep. The patient's maternal aunt had had an operation in the thoracic region of the spine for "tumor," and a suboccipital craniotomy had been performed eight years previously, elsewhere for syringomyelia. This aunt was becoming paralyzed in her feet and was staggering a great deal when she walked. Possibly this unfortunate experience of the aunt, together with the absence of definite objective evidence of involvement of the central nervous system, had led to a diagnosis elsewhere of hysteria in the case of the niece.

On examination at the clinic there was a marked list of the patient's body toward the left with increased prominence of the right hip and scoliosis (fig. 13). Percussion of the right sacroiliac region caused severe pain. All spinal motions were painful, and forward bending of the head on the chest caused pain in the back. Kernig's sign was present and the achilles reflex was absent on the right. Roentgenologic examination of the lumbar and sacral portions of the spine gave negative results. A diagnostic spinal puncture, made through the second lumbar interspace, revealed no evidence of subarachnoid block. However, there was a total protein content of 90 mg per hundred cubic centimeters of spinal fluid, and the globulin test gave a positive result. At the time of diagnostic puncture air was injected into the subarachnoid space in order to localize a suspected intraspinal lesion. The films revealed a defect in the column of air at the fourth lumbar interspace.

¹¹ Love, J. G., and Walsh, M. N. Protruded Intervertebral Disks. Report of One Hundred Cases in Which Operation Was Performed. *J. A. M. A.* **111**: 396-400 (July 30) 1938.

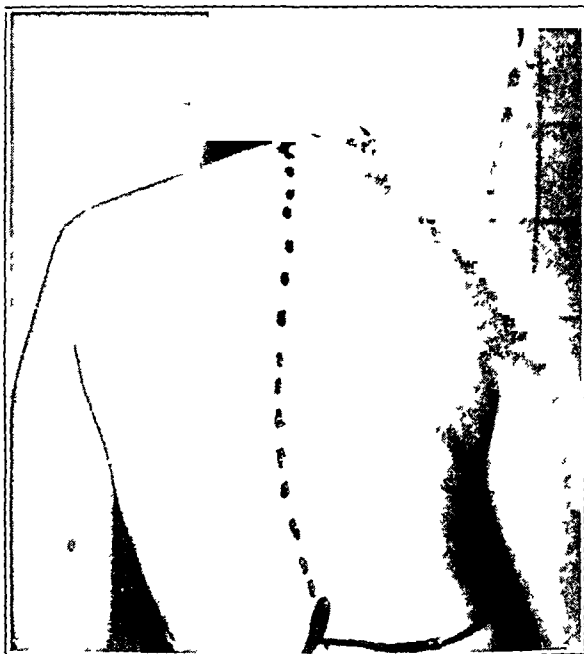


Fig 13—Preoperative photograph of patient, the severe listing of the body and the scoliosis secondary to protrusion of a lumbar intervertebral disk are evident

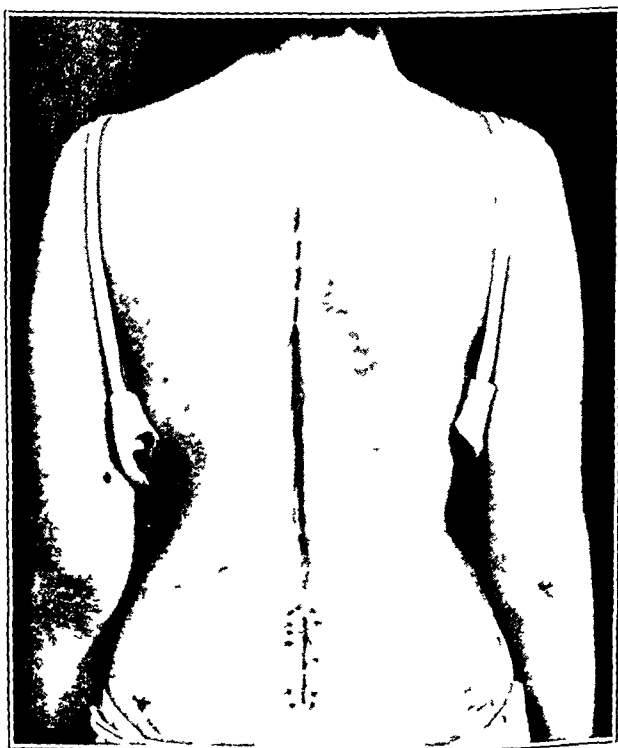


Fig 14—Photograph of patient shown in figure 13, taken fifteen days after removal of a protruded portion of the fourth lumbar disk, the wound is well healed and the scoliosis which had been present prior to operation has disappeared

Partial laminectomy was performed, and after resection of an abnormally thick ligamentum flavum at the fourth interspace, a large protruded fragment of the fourth lumbar disk was removed extradurally. Part of the large fragmented cartilage was removed on the right side and part on the left. The ligamentum flavum at the fifth space was abnormally thickened also, and it was resected, but the lumbosacral disk was normal. The dura mater was not opened. The wound was closed in layers without drainage.

The patient received immediate relief from pain, and at the time of dismissal from our care, on October 27, fifteen days after removal of the protruded portion of the disk, her wound was well healed, her spine was straight and her condition was excellent (fig 14).

PATHOLOGIC CHANGES OBSERVED IN THE HYPERTROPHIED LIGAMENTUM FLAVUM

Since a very definite change is almost constantly seen in the ligamentum flavum that overlies a protruded disk, it is necessary that some consideration be given to this structure whenever the subject of protruded disk is discussed. From the beginning of our work on disks, we have noted various abnormalities of the ligamentum flavum. The changes usually consist of marked thickening, increased firmness and decreased elasticity. On being cut, the ligaments impart an entirely different type of resistance from that encountered in the resection of normal ligamenta flava. Their cut surfaces appear whitish gray rather than yellow.

Dr Dockerty, of our department of pathology, has interested himself in these structures and has favored us with the following preliminary report of his observations. What are the pathologic changes observed in cases of so-called hypertrophy of the ligamentum flavum? The present study is far from complete as regards both surgical material and normal controls selected from the various age groups. On the other hand, certain definite changes seem to occur so consistently that we feel justified in recording them in this preliminary report.

Grossly, the affected ligaments are thicker than normal, they measure 4 to 6 mm in cross section as against an established normal of from 2 to 5 mm. The cut surface, instead of being homogeneously yellow, reveals, in a typical case, white bands running throughout. Microscopically, the changes, seen best with special stains for elastic tissue, are as follows:

- 1 Fragmentation, usually longitudinal, of the elastic tissue fibrils. The ends of these frayed fibrils often appear shriveled.

- 2 Replacement of damaged fibrils by a more primitive type of mesoderm, namely, fibrous connective tissue. In many instances the latter is present in the form of wide bands that run throughout the length of the affected ligament.

3 Blood vessels are few, and those present are small in caliber as a result of the hyaline substance which is deposited within their walls and which replaces the muscularis. This finding leads one to wonder whether vascular damage as a result of trauma may not explain the other changes observed. In three "normal" controls studied to date, vascular changes were not noted, and the ligaments had none of the alterations noted microscopically.

XANTHOMA OF TENDON SHEATHS AND SYNOVIAL MEMBRANES

A CLINICAL AND PATHOLOGIC STUDY

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This paper is a review of the literature dealing with xanthoma and of the cases observed at the Mayo Clinic and an attempt to arrive at certain definite conclusions by which this lesion can be properly classified. Owing to the histologic similarity of the synovial membrane of the tendon sheaths and that of the joints,¹ it was felt that growths involving both these structures should be considered. Other types of solitary xanthoma occur in bone and in subcutaneous tissue, but they will not be discussed in this paper. An effort has also been made to refrain from any reference to the general subject of the xanthomatous diseases except when it is necessary as an aid in establishment of the true nature of these solitary tumors.

HISTORICAL REVIEW

The first reference in the literature to the group of conditions now listed under the general heading of xanthoma was by the French dermatologist, Rayer.² In 1836 he described under the name *plaques*

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Thesis submitted by Dr Galloway to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Orthopedic Surgery

1 Piersol, G A. Normal Histology, with Special Reference to the Structure of the Human Body, ed 15, edited by W H F Addison, Philadelphia, J B Lippincott Company, 1932, pp 63 and 75-76. Bremer, J L. A Text-Book of Histology Arranged upon an Embryological Basis, ed 5, Philadelphia, P Blakiston's Son & Co, 1936, pp 90-91 and 120.

2 Cited by Rowland, R S. Xanthomatosis and the Reticulo-Endothelial System. Correlation of an Unidentified Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome), Arch Int Med 42 611-674 (Nov) 1928, cited by Gruenfeld, G, and Seeng M G. The Nature of So-Called Xanthoma. A Critical Review, Arch Path 17 546-573 (April) 1934.

jaunatices des paupières those yellowish eruptions usually located on the eyelids but occasionally found in other parts of the skin and at present commonly spoken of as xanthoma palpebrarum or xanthelasma, the latter being a term proposed by Wilson³ in 1863, meaning yellow plaques

Lebert,⁴ in 1845, first introduced the term xanthoma and attributed the color of the tumor to a peculiar sort of fat, to which he gave the name xanthos. He was followed in 1869 by Smith,⁵ who again suggested the name xanthoma and spoke of the tumor-like appearance of the yellow nodules. Lebert⁴ recognized these tumors as benign and differentiated them from similar fibrous tumors, especially from sarcomas. In 1851 Addison and Gull⁶ described 4 cases of xanthoma associated with hepatic disease and jaundice, a condition at present designated by the term xanthoma multiplex, and 1 case of xanthoma associated with pancreatic disease, now known as xanthoma diabeticorum. They mentioned involvement of the tendon sheaths of the fingers in 1 of their cases. Involvement of the tendon sheaths was cited also by Fox⁷ and by Carry⁸ in 1897, this was referred to by Fox as the "gout form" of xanthoma.

Tendon Sheaths—1852 to 1890. According to Gruenfeld and Seelig,⁷ Beekman,⁸ King⁹ and Ragins,¹⁰ the first description of solitary xanthoma of the tendon sheaths was published in 1852 by Chassaig-nac,¹¹ who described a nodular lesion on the index and middle fingers of the right hand, and the second was given in 1857 by Spencer Wells,¹²

3 Cited by Rowland, R. S. Xanthomatosis and the Reticulo-Endothelial System. Correlation of an Undifferentiated Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome), *Arch Int Med* **42** 611-674 (Nov) 1928.

4 Cited by Garrett, C. A. Tumors of the Xanthoma Type, *Arch Surg* **8** 890-907 (May) 1924.

5 Addison, T., and Gull, W. On a Certain Affection of the Skin, Vitiligoidea—a Plana, Tuberosa, with Remarks and Plates, *Guy's Hosp Rep* **7** 265-276, 1851.

6 Cited by Thannhauser, S. J., and Magendantz, H. The Different Clinical Groups of Xanthomatous Diseases. A Clinical Physiological Study of 22 Cases, *Ann Int Med* **11** 1662-1746 (March) 1938.

7 Gruenfeld, G., and Seelig, M. G. The Nature of So-Called Xanthoma. A Critical Review, *Arch Path* **17** 546-573 (April) 1934.

8 Beekman, F. Giant-Cell Tumors of the Tendon Sheaths, *Ann Surg* **62** 738-745 (Dec) 1915.

9 King, E. S. J. Concerning the Pathology of Tumours of Tendon-Sheaths, *Brit J Surg* **18** 594-617 (April) 1931.

10 Ragins, A. B. Benign Tumors of the Tendon Sheaths of Unusual Size, *Ann Surg* **93** 683-690 (March) 1931.

11 Cited by Tourneau,¹³

12 Cited by Tourneau,¹³ and by King⁹

who described a similar tumor of the index finger Tourneau,¹³ in 1913, after a review of all the previously reported cases in the literature, classified the growths as fusocellular sarcomas. Since opinion is divided as to their true nature, they have been classified and listed in this paper as probable and not true xanthomas of the tendon sheaths.

It was noted by Paget⁴ in 1853 that the yellow tumors may be found in such places as the subcutaneous tissues, the eyelids, the conjunctiva, the cerebral membranes, the breasts and the uterus but that they are especially connected with bone. In addition, Paget sketched the pathologic picture of these tumors, describing large oval pigmented cells, irregular fragments of cells without a definite cell wall but with many nuclei, typical giant cells and spindle cells. He failed, however, to describe foam cells as such.

As was mentioned by Heurtaux¹⁴ in 1891 and again by Tourneau¹³ in 1913, the first authentic report of yellow giant cell tumor of the tendon sheaths must be accredited to Broca,¹⁵ who, in 1860, described a case in which the tumor involved a tendon sheath of the right hand in a woman 20 years of age, to this type of tumor Broca¹⁵ applied the name *myelome*. His report was followed by the description by Czerny,¹⁶ in 1868, of a similar lesion, located on the right ring finger of a woman 20 years of age and diagnosed by him as *sarcome a myeloplaxes*.

Billroth¹¹ is reputed to have reported an example of this type of tumor in 1868. It was found, however, that he had recorded 3, 1 in which death due to generalized metastasis occurred within about a year, 1 in which the tumor recurred with axillary metastasis and 1 in which the growth involved the flexor tendon sheath of the forearm and death from pyemia followed amputation of the forearm. The first case is, of course, excluded from any consideration here, for it is evident that the tumor was malignant, and it had been listed by Tourneau¹³ as a myxofibrosarcoma. Although in the second case the patient recovered after a second local excision of the growth and excision of the axillary lymph nodes, the inference that the tumor had metastasized must exclude it from this discussion. The lesion in the third case may possibly have been a xanthoma, but all indications would lead one to believe that amputation had been done for a malignant tumor, and, since a reasonable doubt exists, it has been discarded.

The next reports, therefore, of this type of tumor were those of Paquet¹⁵ and Gross,¹⁵ each of whom described 1 case in the year

13 Tourneau, J. P. Les sarcomes des gaines tendineuses, Rev de chir, Paris 47 817-854, 1913

14 Heurtaux, M. A. Myélome des gaines tendineuses, Arch gen de med 167 40-54 (Jan) 1891

15 Cited by Tourneau¹³ and by Heurtaux¹⁴

1878 The growths were associated with the left palm and the right index finger respectively and were designated as *sarcome à myeloplaxes*. To these must be added 2 cases reported by Koenig¹⁶ in 1881, 1 reported by Ferie¹¹ in 1888 and a similar case reported by Labougle and Cas-sart¹¹ in 1890. All of these authors referred to the tumors as belonging to the order of giant cell sarcomas. This makes a total of 8 undoubted tumors of this type reported during the first thirty-one years of the history of the tumor.

During the same period several cases of probable xanthoma were discovered. One was reported by Eichhorst¹¹ in 1876. The patient was a girl 15 years of age whose right leg had been amputated owing to a fusocellular sarcoma of the tendon sheath of the anterior tibial muscle that had been present for three years. One was reported by Markoe¹ in 1884, in which the tumor had recurred after local excision from the tendon sheath of the left great toe, 1 was described by Blum¹¹ during the same year, in which the growth had been present for fourteen years in the flexor tendon sheaths of the sole of the right foot and recovery took place after amputation of the leg, 1 was reported by Reverdin¹¹ in 1885, in which the tumor had been present for ten years and the patient recovered after amputation of the thumb, and by Dumrath¹¹ in 1886, in which the growth had persisted for seven years and the patient recovered after local excision. In addition 2 cases were reported by Mayer¹¹ in 1886, the tumors being diagnosed as sarcoma, in which recovery occurred after conservative surgical intervention. These cases, together with those reported by Chassaignac¹¹ and Spencer Wells¹² and the cases of true xanthomas, make a total of 18 cases reported to the end of 1890.

1891 to 1899 Heurtaux,¹⁴ in 1891, was the first to make a critical study of this subject. He differentiated this group of tumors from the sarcomas and gave them the name of myeloma, after Nelaton,¹⁷ who had previously suggested the name myeloma or medulloma for similar osseous structures observed by him and believed by him to be connected with the skeletal system only. Heurtaux¹⁴ stated that the term myeloma should not be used as a synonym for sarcoma. He recorded 3 personally observed cases in which the lesions were located in the tendon sheaths of the fingers and a fourth case, in which the findings were suggestive but no operation was done.

Dor,¹⁶ in 1898, in his description of a lesion of the right index finger, was the first to describe the xanthoma cell and perhaps the first to con-

16 Cited by Bellamy, H. F. The Myeloid Tumor of Tendon Sheaths, J. Path. & Bact. 7 465-480, 1901.

17 Cited by Heurtaux¹⁴ and by Bellamy, H. F. The Myeloid Tumor of Tendon Sheaths, J. Path. & Bact. 7 465-480, 1901.

clude that these tumors are of inflammatory origin. He also stated the opinion that they are of a mixed type, composed of both myeloid and xanthomatous tissue but having a common cellular origin. As a result of his observations he proposed the term myeloxanthoma.

From 1891 to 1899 inclusive, 13 more cases were described in the literature, in 9 of which the tumors were located on the hands or fingers and in 4 of which they occurred about the ankle or on the toes. One case was reported by each of the following: Pilliet¹¹ (1893), Pilliet and Mauclore¹¹ (1894), Longuet and Landel¹¹ (1895), Bonhomme¹⁸ (1897), Bonjour¹⁸ (1897), Venot¹¹ (1898), Menciere¹¹ (1898), Albertin and Paviot¹¹ (1899) and Arcoletto¹¹ (1899). Two each were reported by Malherbe¹¹ (1896) and Targett¹⁹ (1897). All except Targett classified the tumors as *sarcome a myeloplaxes*. Targett¹⁹, on the other hand, said they had the character of dense fibrosarcoma containing within its stroma large numbers of foreign body giant cells, the presence of which he failed to explain. He reported the growths as malignant spindle cell sarcomas and suggested that they might have originated from some bone-forming membrane. Bonjour¹⁸ concluded that the myeloid tumors form a distinct group of neoplasms with a mother cell probably originating in the medullary tissue of bones. He divided them into three groups: (1) myeloma of the genus epulis, (2) myeloma of tendon sheaths and fibrous tissue and (3) central myeloma of bone. Bonhomme¹⁸ concluded that the tumor in his case was a nonmalignant neoplasm resulting from chronic inflammation of the tendon sheath, possibly due to trauma. These 13 cases added to those already reported make a total of 25 cases of proved xanthoma of the tendon sheaths reported by the turn of the century.

1900 to 1909. The twentieth century opened with the report of 5 cases by Muller,¹¹ in all of which there was involvement of the hand and finger tendon sheaths, and a sixth, by the same author, in which successful excision was done. The tumors in the first 5 cases he diagnosed as giant cell sarcomas and that in the sixth as a melanotic sarcoma (in this paper it has been listed with the probable xanthomas). During the same year, Delbance²⁰ reported a case in which a nodular lesion involved the extensor tendon sheath of the thumb in a man aged 31.

The year 1901 revealed several cases: 1 reported by Tomaselli,¹¹ of a tumor which he called a giant cell sarcoma, 4 reported by Heller,¹¹

18 Cited by Bellamy, H. F. The Myeloid Tumor of Tendon Sheaths, *J. Path. & Bact.* 7: 465-480, 1901, and by Tourneau.¹³

19 Targett, J. H. Giant-Cellled Tumours of the Integuments, *Tr. Path. Soc. London* 48: 230-235, 1897.

20 Cited by Mason, M. L., and Woolston, W. H. Isolated Giant Cell Xanthomatic Tumors of the Fingers and Hand, *Arch. Surg.* 15: 499-529 (Oct.) 1927.

and 5 reported by Bellamy²¹ The tumor in Tomaselli's case was located on a foot, all those in Heller's cases involved the tendon sheaths of fingers, and all his patients recovered after local excision Heller's diagnosis was *sarcome a myeloplaxes* In 4 of Bellamy's cases the growth was connected with the fingers, and in the fifth it involved the palm Bellamy listed as important characteristics of these tumors the presence of adult connective tissue, certain proliferating cells, multinucleated or giant cells, blood vessels with actively proliferating endothelium and, finally, advanced stages of fatty degeneration As a result of this study he concluded that, although these tumors contain large numbers of giant cells, they do not belong among the giant cell tumors but that owing to the fact that their evolution is due to proliferation of the endothelial cells of the blood vessels, they should be called endotheliomas However, since large numbers of giant cells also play a prominent part in the pathologic picture of these growths, he concluded that they should be termed myeloid endotheliomas

In 1902, Martini²² described a giant cell sarcoma which was successfully excised after the second attempt Turner,²³ during the same year, described a myeloma of the tendon sheath of a finger in a young woman resulting from overstrain due to excessive violin practice The following year, Bloodgood²⁴ added 2 cases under the classification of hemangiomatous elephantiasis He later²⁵ regarded the growths in these 2 cases as similar to those under discussion in this paper He added that when these tumors are adherent to or associated with tendon sheaths even above the fingers and toes (on the hand, wrist, foot or ankle) and have the mottled appearance of xanthoma, they can almost always be differentiated from the sarcomas The presence of foam cells, according to him, rules out the diagnosis of sarcoma, as does usually the presence of the foreign body giant cell

Coenen,²⁶ in 1904, employing the term "giant-cell sarcoma of the tendon sheaths," added 6 cases In 5 the tumors were allied with the flexor, and in 1 with the extensor, tendon sheaths of the fingers

In 1905, Malapert and Morichau-Beauchant²⁷ described a giant cell sarcoma of the flexor tendon sheath of the right middle finger

21 Bellamy, H F The Myeloid Tumor of Tendon Sheaths, *J Path & Bact* 7 465-480, 1901

22 Turner, G R A Case of Primary Sarcoma of the Synovial Membrane of the Ankle-Joint, *Tr Clin Soc London* 35 137-138, 1902

23 Bloodgood, J C Haemangiomatous Elephantiasis, *Progres med* 4 154 157 (Dec) 1903

24 Bloodgood, J C Xanthomas, *Arch Surg* 8 882-889 (May) 1924

25 Malapert, P, and Morichau-Beauchant, R Sarcome a myeloplaxes de la gaine synoviale du flechisseur du medius, *Bull et mem Soc anat de Paris* 80 390 (May) 1905

which presented no evidence of recurrence after amputation of the finger. In the same year, Suter²⁶ recorded a digital tumor for which amputation of the distal phalanx was done owing to erosion by the tumor of a portion of that phalanx.

Gaudiani,¹¹ in 1906, described 2 tumors. One of them was found by Tourneux¹⁸ to be a melanotic giant cell sarcoma. It was located on the flexor tendon sheath of the right ring finger, had been present for twelve years and showed no recurrence after local excision, it is, therefore, classified in the present paper with the probable xanthomas. The other was diagnosed by Gaudiani¹¹ as a giant cell sarcoma of the extensor tendon sheath of the left great toe and was successfully excised from a girl 12 years of age. Bazy,¹¹ in 1907, followed with another, and in 1908 Fritsch¹¹ added 2 more, all of which received the name of giant cell sarcoma, or *sarcoma à myeloplaxes*.

Seven cases were reported by Lenzi and Abetti¹¹ in 1909. The tumors in 6 involved the flexor tendon sheaths of the fingers and that in 1 the extensor tendon sheath of a foot. The growths were classified as giant cell sarcomas. In the same year Kammer²⁷ cited 2 cases. In 1 the tumor was situated on a finger, and in the other, on a toe.

During this period (1900 to 1909) 41 cases of undoubted xanthoma of the tendon sheaths were reported, bringing the total up to 66. However, there is 1 case of probable xanthoma that might be added, it was reported by Nony¹¹ in 1909. The tumor was successfully excised from the flexor tendon sheath of the left forearm and was diagnosed as a globocellular sarcoma.

1910 to 1919. Under the term myeloma, Mathews,²⁸ in 1911, reported a case of tumor of the flexor tendon sheath of the index finger, and during the same year Russell²⁹ added another.

In 1912, Hedinger³⁰ reported 4 cases but gave no details concerning them except the age and sex of the patients. The following year, Spiess³¹ added 4 cases and suggested the name *Hemosiderin Sarcoma*.

26 Suter, F. A. Zur Casuistik der Fingertumoren, Arch f klin Chir **75** 624-628, 1905.

27 Cited by Smith, C. The Histology and Nature of So-Called Foam-Cell Tumors with a Report of Four Cases of Endothelioma Xanthomatousum, Surg, Gynec & Obst **14** 551-557 (May) 1912.

28 Mathews, F. S. Myeloma of the Tendon Sheath, Ann Surg **53** 847-848 (June) 1911.

29 Russell, J. I. Sarcoma of the Tendon Sheath of the Flexor Longus Pollicis Muscle, Ann Surg **53** 285-286 (Feb) 1911.

30 Hedinger. Zur Frage der sogenannten Myelome der Sehnenscheiden. Centralbl f allg Path u path Anat **23** 904 (Oct 31) 1912.

31 Spiess, P. Zur Lehre der von Sehnenscheiden und Aponeurosen ausgehenden Riesenzellensarkome, Frankfurt Ztschr f Path **13** 1-44, 1913.

gigantocelluläre xanthomatodes der Sehnnenscheiden und Aponeurosen
He added that pathologically a chronic granulation process can be safely excluded, that the tumors are definitely benign and that they resemble epulis to a considerable extent.

The term granuloma made its appearance in 1913, when Fleissig³² described 3 growths located on the fingers. He pointed out that these tumors lack the principal diagnostic points of neoplasms, such as polymorphism, polychromatophilia, destructive invasion of the surrounding tissues and mitosis, and asserted that they are benign. The same year, Le Filliatre³³ added 1 more case to the increasing list.

Grant and Stewart,³⁴ in 1914, described a nodular lesion that had recurred after local excision in the tendon sheath of a finger. They regarded it as a myeloid endothelioma and emphasized the important role that trauma plays in the causation of this variety of tumor. Using the name "pigmented giant-cell xanthosarcoma," Landois and Reid,³⁵ in this same year, reported 4 personally observed cases and a fifth observed by Robinson, of Clifton Springs, New York. Two of their cases had already been reported by Bloodgood²³ in 1903, which leaves only 3 new cases to their credit.

In 1915, Stewart and Flint³⁶ described 2 tumors, 1 on the flexor surface of the right thumb and the other on the flexor surface of the left wrist. During that year, Beekman added 3, 2 located on fingers and 1 on a great toe. He also reviewed the literature and, after a consideration of the preexisting data, concluded that it had not been definitely proved that these tumors are caused by inflammation or chronic irritation. He stated, however, that they certainly do not belong under the classification of sarcoma. He stated that histologically they resemble giant cell epulis more than any other type of giant cell tumor (although they do not arise from the periosteum as does epulis) and that they further resemble epulis in that they do not recur after complete removal and never metastasize. He then suggested the name "giant-cell sarcoid tumors of the tendon sheaths." He agreed with Bloodgood²³ that the term giant-cell tumor is well established and should not be dropped.

32 Fleissig, J. Ueber die bisher als Riesenzellensarcome (Myelome) bezeichneten Granulationsgeschwulste der Sehnnenscheiden, *Deutsche Ztschr f Chir* **122** 239-265, 1913.

33 Le Filliatre. Sarcome à myeloplaxes de la gaine du jambier postérieur. *Bull et mem Soc anat de Paris* **88** 222-224, 1913.

34 Grant, T. P., and Stewart, M. J. On Myeloid Tumors of Tendon Sheath with Report of a Case, *Glasgow M J* **81** 333-339, 1914, abstracted, *Internat Abstr Surg* **19** 225 (Sept) 1914.

35 Landois, F., and Reid, M. Das pigmentierte riesenzellenhaltige Xantho-Sarkom der Extremitäten, *Beitr z klin Chir* **95** 56-73 (Dec) 1914.

36 Stewart, M. J., and Flint, E. R. Observations on the Myeloid Tumor of Tendon Sheaths, *Brit J Surg* **3** 90-99, 1915-1916.

In 1917, Pybus³⁷ reported a nonrecurring myeloid tumor of the flexor tendon sheath of the right little finger

One of us (Broders),³⁸ in his paper published in 1919, described 17 tumors, 1 of which was located in the subcutaneous tissue on the anterior surface of the leg, midway between the knee and the ankle, and was not related to any tendon sheath. This tumor will not be considered with the remaining 16, 10 of which were situated on the upper extremity and 6 on the lower. He described the macroscopic and microscopic appearance of the growths and suggested that the purpose of the foreign body giant cell is to absorb foreign material, in other words, it is a "clean-up cell." He spoke also of its morphologic similarity to the osteoclast and expressed the opinion that its function may be the same. In addition, he brought out the resemblance of these giant cells to those found in the medullary giant cell tumor of bones and gums, to those that collect around cholesterol crystals, blood pigment, nonabsorbable suture material and colloid and cornified epithelium in cases of epithelioma and to those associated with syphilis, leprosy, blastomycosis, coccidioid granuloma and tuberculosis.

The decade from 1910 to 1919 revealed that 40 more undoubted xanthomas of the tendon sheaths had been recorded, making the total to the end of the decade 106. Two probable xanthomas were also seen, 1, reported by Gignoux¹¹ in 1911, was situated on a flexor tendon sheath near the malleolar region of the right foot and had been present for seven years. Recovery took place after amputation of the leg. The other was described by Jourdan and Etienne¹¹ in 1911. It was located in the tarsal region and had likewise been present for seven years. Both of these growths were diagnosed as globocellular sarcomas.

1920 to 1929. Krogus,³⁹ in 1922, suggested the name "xanthosarcoma" and described 4 cases, in 2 the lesion was on the lower extremity and in 2 it occurred on the upper. He expressed the opinion that, although growths located on the fingers are benign those on the hands, forearms and feet are apt sooner or later to reveal a more malignant nature. During the same year, Kaufmann²⁰ reported 3 cases and Seyler⁴⁰ described 10, using the name of "xanthomatous granuloma." Of the tumors described by Seyler only 1 involved a tendon sheath. One was in a joint, and the remainder were subcutaneous,

37 Pybus, F. C. A Note on a Case of Myeloma of the Tendon Sheath, *Brit J Surg* 5 172-173, 1917

38 Broders, A. C. Benign Xanthic Extraperiosteal Tumor of the Extremities Containing Foreign Body Giant Cells, *Ann Surg* 70 574-581 (Nov.) 1919

39 Krogus, A. So-Called Xanthosarcoma of Tendon Sheaths, *Finska Lak-sällsk handl* 44 102, 1922, abstracted, *Internat Abstr Surg* 35 415-416 (Dec.) 1922

40 Seyler. Ueber xanthomatöse Granulome, *Virchows Arch i path Anat* 239 20-31, 1922

1 located over the bridge of the nose, 1 about the temporal region, 1 on an ulnar nerve, 3 on the leg and 2 on the arm

In 1923, Hartert⁴¹ described 5 tumors which he called xanthosarcomas. Three were located on the feet and legs and 2 on the tendon sheaths of the fingers. About the same time, Buxton⁴² reported a case which he had personally observed and 1 which he had collected from the Royal College of Surgeons. Buxton called both tumors "giant-cell myelomas" but distinguished them from sarcomas. He quoted Shattock as saying that these myelomas of tendon sheaths are the same as those found at the ends of the long bones. Shattock had suggested also that they are due to embryonic displacement of osseous elements into the tendon sheath, which is continuous with the bone, and that these displaced elements are related to the bone marrow.

Garrett,⁴³ in 1924, under the subtitle "fibrohemangioma," described 19 of the 76 recorded as xanthomatous. All of these 19 tumors contained foreign body giant cells, and 9 revealed the presence of foam cells. Two of the cases had already been reported by Bloodgood²³ in 1903. Garrett⁴³ did not specify the exact location of the tumors in the remaining 17 and as many or all of them may not have been associated with tendon sheaths, they were not included in the present paper. Using the subtitle "fibroma of tendon sheaths," Garrett also concluded that 13 of the total number of 30 were xanthomas. Of the remaining 17 in this group, all are reported as containing foreign body giant cells and pigment, and the similarity, in some respects, to the 13 considered to be xanthomas is noted. The differences between these two groups appear so slight that it is inconceivable that two distinct divisions could be made of them, and therefore they are all included in the present paper under the classification "xanthoma of tendon sheaths." Under the subtitle "granulation-tissue tumors," 1 lesion of the recorded 26 is considered to be xanthomatous in structure, and it contained foreign body giant cells, foam cells and pigment, but here again Garrett failed to locate the tumor, and since the location is not known the case is also excluded from the present paper. In addition, Garrett concurred in Bellamy's²¹ opinion that tumors of this type are endotheliomas and stated that they are benign.

Dyke,⁴⁴ in 1924, reported 2 cases of tumor diagnosed as myeloma. He expressed the idea that the presence of giant cells is to be considered

41 Cited by Janik, A. Tumors of Tendon Sheaths, *Ann Surg* 85 897-911 (June) 1927

42 Buxton, St J D. Tumours of Tendon and Tendon Sheaths, *Brit J Surg* 10 469-474 (April) 1923

43 Garrett, C A. Tumors of the Xanthoma Type, *Arch Surg* 8 890-907 (May) 1924

44 Dyke, S C. On the Significance of Anisotropic Fatty Substances in Myelomatous Tumours, *J Path & Bact* 27 5-10, 1924

as evidence of the endothelial nature of these myelomatous tumors and, similarly, that the presence of foam cells containing dioplets of anisotropic fat substance, probably cholesterol ester, is still further evidence of their endothelial origin. Weber,⁴⁵ in the same year, presented a case of xanthomyeloma of the tendon sheath and expressed the opinion that these tumors are associated with constitutional hypercholesteremia. Miller⁴⁶ called the lesion that he reported in the same year a xanthoma of the tendon sheath. Lecène and Moulonguet,⁴⁷ in 1924, reported 3 cases, 2 of the tumors being located on the fingers and 1 on a foot. They expressed the opinion that this tumor is a *tumeur d'origine dystrophique* and accepted the conservative method of treatment as that of choice.

The tumor described by Vermooten⁴⁸ in 1925 involved the proximal phalanx of the right thumb and was a typical xanthoma. It may well be that this tumor first involved the tendon sheath and secondarily invaded the diaphysis of the bone. Since it is not known whether this tumor was primary in the tendon sheath, it was not included in the present paper.

In 1927, Mason and Woolston⁴⁹ reviewed the previous literature, reported numerous cases from the records of others and added 8 personally observed cases of what they called "giant-cell xanthomatous tumor." They emphasized the benign character of this type of growth and discussed the clinical and pathologic picture, but they advanced no new ideas concerning its causation or pathogenesis. Janik,⁵⁰ in 1927, reported 14 cases collected from the literature, which have already been alluded to here. In the same year, Harbitz⁵¹ described 11 new cases and after a review of the literature came to the conclusion that the growths should be classified as real tumors, probably sarcomas but comparatively benign.

45 Weber, F. P. Cutaneous Xanthoma and "Xanthomatosis" of Other Parts of the Body—Pituitary Xanthomatosis—"Xanthomyelomata" of Tendon-Sheaths, etc.—and the "Cholesterol Diathesis," *Brit J Dermat* **36** 335-370 (Aug-Sept) 1924.

46 Miller, E. M. The Surgical Aspect of Xanthoma Tumors, *Ann Surg* **80** 256-267 (Aug) 1924.

47 Lecène, P., and Moulonguet, P. Les tumeurs à myélopлаxe des gaines tendineuses, *Ann d'anat path* **1** 393-411 (July) 1924.

48 Vermooten, V. Xanthosarcoma of Thumb. A Central Benign Giant-Cell Tumor of the Proximal Phalanx of the Thumb, *Ann Surg* **81** 851-856 (April) 1925.

49 Mason, M. L., and Woolston, W. H. Isolated Giant Cell Xanthomatic Tumors of the Fingers and Hand, *Arch Surg* **15** 499-529 (Oct) 1927.

50 Janik, A. Tumors of Tendon Sheaths, *Ann Surg* **85** 897-911 (June) 1927.

51 Harbitz, F. Tumors of Tendon Sheaths, Joint Capsules and Multiple Xanthoma, *Arch Path* **4** 507-527 (Oct) 1927.

Segovia and Llompert,⁵² in 1928, reported 2 tumors of the flexor tendon sheaths of the hand, and in the following year Eisen⁵³ and Kurtz⁵⁴ each described 1, both of which were located on an upper extremity. Eisen described his as a giant cell tumor and concluded that the accompanying bony defect observed in the proximal phalanx of the index finger was due to pressure from the tumor and not to an infiltrative process, for it was completely filled in with new bone twenty months later. Kurtz⁵⁴ expressed the opinion that the benign character and structure of this variety of tumor suggest that it may arise from a local inflammatory process connected with trauma and some peculiar disturbance of local lipid metabolism.

During the same year, Geschickter and Copeland⁵⁵ added 27 cases collected at the Johns Hopkins Hospital. Two of these had already been reported by Bloodgood²³ in 1903 and 2 by Landois and Reid³⁰ in 1914. One patient in this group had 2 tumors involving the flexor tendon sheaths of the index and ring fingers, making a total of 24 tumors. Geschickter and Copeland⁵⁵ advanced the opinion that this type of tumor is derived from the sesamoid bones. They cited Pfitzner, who had shown that the sesamoids are most frequent on the first, second and fifth digits of the hand and foot, at the metacarpophalangeal or metatarsophalangeal joints, where giant cell tumors of the tendon sheaths are most commonly found but that they may occur at the sites of these joints or the interphalangeal articulations in any of the fingers and toes. Other sites for the sesamoids may be in the tendons about the elbow, knee or ankle, in the tendon of the psoas muscle at the pubis and occasionally in the tendon of the gluteus maximus muscle near the head of the great trochanter. They continued "When giant cell tumors of the tendon sheaths are examined microscopically a variant of the typical giant cell structure is seen, characterized by an unusual amount of pink-staining fibrous tissue, enclosing in a network cells of the cartilage type. This fibroid substance on further investigation is identified as the vestige of white fibrocartilage from which the sesamoid bones are derived." Tumors studied by them which did not occupy the site of these bones did not show the characteristic giant cell structure, and they concluded, therefore, that such growths should be classified as fibrohemangiomas, fibromas or ganglions.

52 Cited by Gonzalez-Aguilar, J. Contribution to the Pathology of Tendon Tumors of Giant Cells, *J. Bone & Joint Surg.* **12** 280-288 (April) 1930.

53 Eisen, D. Giant-Celled Tumors of Tendon Sheaths, *Am. J. Surg.* **7** 120-123 (July) 1929.

54 Kurtz, A. D. Xanthoma of Tendon Sheath, *Am. J. Surg.* **7** 862-864 (Dec.) 1929.

55 Geschickter, C. F., and Copeland, M. M. Osteitis Fibrosa and Giant Cell Tumor. *Arch. Surg.* **19** 169-271 (Aug.) 1929.

During the period from 1920 to 1929, 99 undoubted xanthomas of the tendon sheaths were reported in the literature. This group, added to the previously reported 106, makes a total to the end of 1929 of 205.

1930 to 1938. In 1930 three authors each reported 1 tumor and listed it as a giant cell tumor of the tendon sheaths. Bessesen's⁵⁶ tumor, which had appeared after an injury, was situated on the right middle finger. Dudley's⁵⁷ was located on the left ring finger. The third tumor, reported by Gonzalez-Aguilar,⁵⁸ was attached to the infra-patellar tendon and is the only tumor in that location that has been described in the literature up to the present time.

Ragins,¹⁰ in 1931, recorded 2 more growths, both located on the feet. He felt that they should be known as benign tumors of the tendon sheaths but added that if giant cells and foam cells had been present they would have been classified as benign xanthomatous giant cell tumors of the tendon sheaths. He stated the opinion that the tumor is a true neoplasm of mesothelial origin, not a granuloma and not associated with a generalized disturbance of cholesterol metabolism or hypercholesteremia.

Six additional tumors were reported in 1932, 1 by Gorog,⁵⁹ who expressed the opinion that it should be listed as a true neoplasm and not as a granuloma. Bellelli⁶⁰ reported a tumor located on the dorsum of the left wrist, Einaudi,⁶¹ 2 growths which he called giant cell tumors and which were allied with the tendon sheaths of the ring finger and the popliteal space. He expressed the belief that the presence of xanthoma cells in such tumors is the result of a disturbance in cholesterol metabolism. Jebens,⁶² retaining the term myeloma, recorded a growth situated on the flexor and extensor tendon sheaths of the left little finger,

56 Bessesen, D. H. Xanthoma, So-Called Giant Cell Tumor of the Tendon Sheath. Case Report, *West J Surg* **38** 701, 1930, abstracted, *Am J Cancer* **15** 1894 (July) 1931.

57 Dudley, H. D. Giant Cell Tumors of Tendon Sheaths, *Northwest Med* **28** 217-219 (May) 1930.

58 Gonzalez-Aguilar, J. Contribution to the Pathogeny of Tendon Tumors of Giant Cells, *J Bone & Joint Surg* **12** 280-288 (April) 1930.

59 Gorog, D. Ueber die Riesenzellengeschwulste der Sehnenscheiden, *Centralbl f allg Path u path Anat* **53** 341-347 (Jan) 1932.

60 Bellelli, F. Su di un tumore delle guaine tendinee, *Riforma med* **48** 630-635 (April 23) 1932.

61 Einaudi, M. Sui tumori a cellule gigante delle guaine tendinee, *Minerva med* **1** 702-708 (May 19) 1932, abstracted *Am J Cancer* **18** 785 (July) 1933.

62 Jebens, E. H. Myeloma of Tendon Sheath, *Proc Roy Soc Med* **25** 1098-1099, 1932.

and he refused to accept the hypothesis of the inflammatory origin of this tumor. The sixth tumor was reported by Sprenger,⁶³ a German writer.

Canavero,⁶⁴ in 1934, added 2 digital tumors. Duany⁶⁵ reported 3, 2 involving the tendon sheaths of the fingers and 1 fastened to a semitendinosus sheath. In the same year, Geschickter and Lewis⁶⁶ added 23 more. The exact details concerning these tumors are lacking, but the authors stated that the majority were located on the fingers, near the metacarpophalangeal and interphalangeal joints, usually on the flexor surface, and that remainder were found chiefly on the hands or about the ankles and feet. They again advanced the hypothesis that these tumors are derived from the sesamoid bones. Morton⁶⁷ also recorded 6 tumors during that year, 4 appeared on the tendon sheaths of the fingers and 2 on the tendon sheaths about the ankle. He classified them under the general heading of synoviogenic tumors having their origin in the synovial membrane of tendons, bursae, joint capsules and joint linings.

In 1935, Bussebaum⁶⁸ added 2 cases and said that these tumors are benign granulation tumors that develop in the same way as does any inflammatory growth. The following year, Wahlgren⁶⁹ described 19 additional tumors, reports of 9 having been collected from Bergstrand. Thirteen of these tumors involved tendon sheaths and 6 the synovial membranes of joints. Of the 13 tumors involving tendon sheaths 1 patient had 2, 1 on the left first and 1 on the left fourth toe. Zumtobel,⁷⁰ in 1936, recorded 4 more tumors and stressed their benign character but denied that they had any relation to trauma or infection.

63 Sprenger, W. Zur Kenntnis der xanthomatösen Riesenzellgranulome der Sehnencheiden, *Arch f klin Chir* **169** 683-687, 1932.

64 Canavero, M. Contributo allo studio e alla conoscenza dei tumori delle guaine tendinee, *Policlinico (sez chir)* **41** 341-361, 1934.

65 Duany, N. P. Tumores de las vainas tendinosas y tendones, *Rev de med y cir Habana* **39** 780-790, 1934.

66 Geschickter, C. F., and Lewis, D. Tumors of Tendon Sheaths, Joints and Bursae, *Am J Cancer* **22** 96-126 (Sept) 1934.

67 Morton, J. J. Tumors of the Tendon Sheaths. Their Close Biological Relationship to Tumors of the Joints and Bursae, *Surg, Gynec & Obst* **59** 441-452 (Sept) 1934.

68 Bussebaum, G. A Contribution on Inflammatory Tumors Presenting the Picture of Malignant Tumors, with a Consideration of So-Called Giant-Cell Sarcoma of the Tendon Sheaths, *Dissert., Halle-Wittenberg*, 1935, abstracted, *Internat Abst Surg* **62** 368 (April) 1936.

69 Wahlgren, F. Ueber die von Sehnencheiden und Gelenkkapseln ausgehenden sog Riesenzelltumoren mit besonderer Berücksichtigung der Pathogenese, *Acta path et microbiol Scandinav*, 1936, suppl 26, pp 77-89.

70 Zumtobel, M. Beitrag zur Klinik und Pathologie der gutartigen Sehnencheiden-tumoren mit besonderer Berücksichtigung der xanthomatösen Riesenzellgeschwulste, *Deutsche Ztschr f Chir* **247** 501-516 (Sept 7) 1936.

Gomori⁷¹ added another, found on the second toe of a woman 30 years of age. He stated that these locally situated tumors that have such a great similarity to giant cell tumors of bone are never associated with any alteration in cholesterol metabolism.

Pique, Brachetto-Brian and Fasciolo,⁷² in 1937, described 2 more tumors, both in women and attached to the tendon sheaths of the thumb and the anterior surface of the wrist. The authors classified them as benign tumors containing giant cells.

In 1938, Thannhauser and Magendantz⁷³ gave an excellent review of the general subject of xanthomatous lesions and presented 2 cases of tendon sheath involvement. The patient in the first was a woman with multiple nodular involvement of the fingers, ankles and right elbow. The patient in the second was a man, a brother of the former patient, who had a xanthoma of the extensor tendon sheath of the right fourth finger and also xanthomatous involvement of both achilles tendons with associated arthritic nodules in the fingers. Thannhauser and Magendantz⁷³ classified these tumors under the heading of the primary essential xanthomatoses.

Lasher,⁷⁴ in 1938, described a xanthoma attached to the extensor tendon sheath of the right middle finger in a woman 53 years of age. The tumor had been present for eight years, it was successfully excised.

From 1930 until 1938, 70 more undoubted xanthomas of the tendon sheaths were cited in the literature. These, together with the 205 already reported, make a grand total of 275 reported since the first case of Broca¹⁵ in 1860 and cover a period of seventy-nine years, making an average of about three to four each year. Of the probable xanthomas 16 have been listed.

Synovial Membranes—1865 to 1899. The first xanthoma of the synovial membrane of the joints was reported by Simon⁷⁵ in 1865. This tumor was of the solitary, pedunculated variety and was successfully excised from the knee of a man 46 years of age. Microscopically

71 Gomori, G. Three Uncommon Tumors, *Am J Surg* **33** 150-156 (July) 1936.

72 Pique, J. A., Brachetto-Brian, D., and Fasciolo, J. C. Tumores benignos de las vainas tendinosas digitales, *Rev ortop y traumatol* **7** 169-181 (Oct) 1937.

73 Thannhauser, S. J., and Magendantz, H. The Different Clinical Groups of Xanthomatous Diseases. A Clinical Physiological Study of 22 Cases, *Ann Int Med* **11** 1662-1746 (March) 1938.

74 Lasher, W. W. *Industrial Surgery. Principles Problems and Practice*. New York, Paul B. Hoeber, Inc., 1938, p. 46.

75 Cited by Hartman, F. W. Synovial Membrane Tumors of Joints, *Surg, Gynec & Obst* **34** 161-167 (Feb) 1922, and by Razemon, P. and Bizard, G. Les tumeurs primitives des articulations. *Rev de chir*, Paris **69** 229-266 1931.

it revealed pigmented cells, large giant cells and foam cells and was diagnosed as a hypertrophied sarcomatous synovial fringe. The next one to appear was described by Annandale⁷⁶ in 1886. It too was a pedunculated growth and was classified as a myeloid sarcoma, but no recurrence followed local excision. In 1886, Weir⁷⁷ added another pedunculated giant cell sarcoma located in the synovial membrane of a knee.

1900 to 1909. The first diffuse xanthoma was reported by Moser⁷⁸ in 1903. It involved the synovial membrane of the left tibiotarsal articulation. Moser called this tumor a giant cell sarcoma. It was an extensive lesion and was successfully excised. There was no evidence of recurrence after seven years of observation.

1910 to 1919. Dowd,⁷⁸ in 1912, under the title "villous arthritis of the knee," was the first writer to describe a diffuse xanthoma of the synovial membrane of the knee. This lesion occurred in a man aged 33 who had had swelling and moderate disability of the knee for four years. When the joint was opened, marked hypertrophy of the membrane was seen, one piece measuring 2 by 1.5 inches (5 by 4 cm). The patient recovered after excision of many of the villi. In spite of this, the author diagnosed the growth as a giant cell sarcoma, but it seems likely that now it would be classified as a xanthoma, and it will be considered as such in this article.

In 1914, 1 additional pedunculated tumor of the tarsal joints was reported by Weil,⁷⁹ and in 1917, Zullig⁷⁹ added a diffuse xanthoma of the right knee.

1920 to 1929. In 1921, Blanco,⁸⁰ at the Mayo Clinic, reported a pedunculated growth arising in the synovial membrane of the left knee and emphasized its similarity to the tumors described by Broders⁸¹ as benign xanthic extraperiosteal foreign body giant cell tumors of the extremities involving tendon sheaths.

A review of the literature was published by Hartman⁸¹ in 1922, and to the cases recorded he added 1 observed by him. The patient was a

76 Cited by Turner, A. L. Primary Sarcoma of the Synovial Membrane. *Lancet* 2:54 (July 7) 1894.

77 Cited by Hartman, F. W. Synovial Membrane Tumors of Joints, *Surg., Gynec. & Obst.* 34:161-167 (Feb) 1922.

78 Dowd, C. N. Villous Arthritis of the Knee (Sarcoma), *Ann. Surg.* 56:363-365 (Aug) 1912.

79 Cited by Razemon, P., and Bizard, G. Les tumeurs primitives des articulations, *Rev. de chir., Paris* 69:229-266, 1931.

80 Blanco, P. Giant Cell Tumor in the Knee Joint. Report of a Case, *J. Orthop. Surg.* 3:156-157 (April) 1921.

81 Hartman, F. W. Synovial Membrane Tumors of Joints, *Surg., Gynec. & Obst.* 34:161-167 (Feb) 1922.

man 20 years of age. Symptoms had been present for four years. Frequent aspirations of bloody fluid from the knee had been done for some time prior to operation. Haitman⁸¹ concluded that it seemed best to place these lesions with the benign tumors of connective tissue origin, and he preferred the name myeloid tumor. He stated, however, that there is always a potentiality of malignancy. In addition, he discussed the pathologic picture and stated that three types of cells are observed microscopically—namely, round cells, foreign body giant cells and foam cells. He added, "Too much importance has been given the foam cell and the giant cell in the classification of this group since both may be absent from otherwise typical tumors arising in the synovia."

Seyler,⁴⁰ in the same year, added a tumor (under the name of *xanthomatische Granulome*) which was located in one of the tarsal joints.

In 1923, 2 more tumors of the local variety were observed, one by Muhe,⁷⁹ in the synovial membrane of the tarsal joints, the other by Paire and Bruas,⁸² situated in the left knee.

Garrett,⁴³ in 1924, reported 3 cases, but from his article one receives the impression that the tumors involved not only the synovial membrane but the bony articulations, and it is difficult to say whether they were true xanthomas, primary in the synovial membrane, they were, therefore, discarded from this review. During the same year another pedunculated xanthoma was reported by Largiader,⁷⁹ which involved the synovial membrane of a knee. The following year two more circumscribed tumors were reported, one by Wustmann⁸³ and the other by Kuozkowski.⁷⁹

Judy,⁸⁴ in 1926, recorded a diffuse xanthoma of the left knee that had resulted from the intra-articular injection of 2 per cent solution of formaldehyde three years prior to synovectomy. Koch⁸⁵ observed a similar tumor that had recurred after a partial synovectomy.

Harbitz⁵¹ in 1927 described a diffuse xanthoma in a woman 20 years of age. The tumor, he stated, resembled the xanthosarcomas of

82 Cited by Faulkner, D. M. Primary Synovial Membrane Tumors of Joints, Surg., Gynec. & Obst. **53** 189-195 (Aug.) 1931.

83 Wustmann, O. Beiträge zur Frage der xanthomatösen Riesenzellneubildungen, Deutsche Ztschr. f. Chir. **192** 381-400 (Aug.) 1925, abstracted J. A. M. A. **85** 1100 (Oct. 3) 1925.

84 Judy, J. A. Discussion, Boston M. & S. J. **194** 28-29 (Jan. 7) 1926.

85 Cited by Razemon, P., and Bizard, G. Les tumeurs primitives des articulations, Rev. de chir., Paris **69** 229-266, 1931, and by Kling, D. H. and Sarlin, D. Hemorrhagic Villous Synovitis of the Knee Joint Due to Xanthoma. Report of a Case, Arch. Surg. **30** 52-61 (Jan.) 1930.

the tendon sheaths Included in the reports of 1927 were 2 more lesions, a diffuse type seen by Herscheiner,⁷⁹ and one of the local variety recorded by Tobler⁷⁹ Both involved the synovial membrane of the knee

The literature in 1928 revealed 6 additional growths, 3 of which, pedunculated and occurring in the knee, were reported by Abadie,⁸⁶ Wegelin⁷⁹ and Simon⁷⁵ respectively Two were of the diffuse form, 1 was reported by Frangenheim,⁷⁹ and the other by Mandl⁸⁷ The sixth, a pedunculated tumor of the ankle, was reported by Paire and Talbot⁸⁸ Similarly Simon⁷⁵ described a pedunculated tumor in the right knee of a man 59 years of age Paire and Talbot⁸⁸ described these tumors as made up of dense inflammatory tissue in which are seen three types of cells giant cells varying between those of bone and those seen in a tubercle macrophagocytes containing blood pigment and lipoid or xanthoma cells

In 1929, Negrie and Canton⁸⁹ added another circumscribed tumor of the knee in a man aged 20 which they felt to be a benign giant cell tumor of the synovial membrane During the same year, Sundt⁹⁰ recorded a synovectomy done for the removal of a diffuse xanthoma, similarly located

1930 to 1938 In 1930, Sonntag⁹⁰ reported a recovery from a simple excision of a pedunculated tumor in a knee

Faulkner,⁹¹ in 1931, reviewed the literature and added to the xanthomas recorded 2 tumors of the synovial membrane of the knee These tumors were pedunculated and large He reserved for them the French term, used by Heurtaux, Talbot and others, *tumeur a myeloplaxes*, or myeloplaxoma He discussed the pathologic picture of these growths and emphasized Talbot's description as an accurate one He added that there is no histologic evidence of malignancy but concluded that if recurrence takes place after conservative operation a high amputation should be done immediately

86 Abadie, J Tumeur a myeloplaxes de la synoviale du genou Tumeur a myeloplaxes de la rotule Accessoirement, une vieille erreur de pronostic, Bull et mem Soc nat de chir **54** 341-346, 1928

87 Mandl, F Cited by Kling, D H, and Sashin, D

88 Cited by Faulkner, D M Primary Synovial Membrane Tumors of Joints, Surg, Gynec & Obst **53** 189-195 (Aug) 1931, and by Razemon, P, and Bizard G Les tumeurs primitives des articulations, Rev de chir, Paris **69** 229-266, 1931

89 Negrie and Canton Tumeur a myeloplaxes de la synoviale du genou Bull et mem Soc nat de chir **55** 617-619, 1929

90 Sonntag Ueber intraartikulare Xanthome des Knees, Deutsche Ztschr f Chir **223** 346-359 (March) 1930

91 Faulkner, D M Primary Synovial Membrane Tumors of Joints Surg Gynec & Obst **53** 189-195 (Aug) 1931

In the same year, Razemon and Bizard⁹² reviewed and discussed all the benign and malignant tumors of the synovial membrane. Of the 45 benign tumors they found 26 to be xanthomatous, they failed, however, to add any new cases of their own. They again emphasized the three typical histologic findings, foam cells, foreign body giant cells and collections of ochre pigment, and expressed the view that small trauma plus minute hemorrhages is the basis for the evolution of these growths.

In 1933, Bonn⁹³ added a diffuse growth observed in a woman 26 years old. It involved the synovial membrane of the left knee and resulted from a previous injury. He pointed out that xanthomatous deposits may occur in any tissue when there is an excess of total blood lipid and that such deposits are likely to occur in granulation tissue.

Kling and Sashin,⁹⁴ in 1935, reported the result of a synovectomy done for "hemorrhagic villous arthritis of the knee joint due to xanthoma." They also reviewed the literature and concluded that these tumors are benign.

Wahlgren, in his article on both the "tendon sheath type" and the "synovial membrane type" of xanthoma, added 6 more, 5 involved the knee and 1 the right tibiotarsal articulation.

In 1936, Geschickter and Copeland⁹⁵ recorded 4 xanthomatous lesions within the synovial membrane of the knee and a fifth about the elbow joint and associated with diabetes. They explained that xanthomatous giant cell tumors of joints are histologically similar to giant cell tumors of tendon sheaths, basing this opinion on the following explanation:

The original condensation for the future sesamoid bone buds from the joint side of the future bone, just beneath the tendinous attachment. An abortive formation of this sesamoid type, undergoing resorption by giant-cell proliferation, may give rise to a xanthomatous giant-cell tumor within the joint. Later when the same embryonic sesamoid focus has migrated to its final position within the tendon sheath a similar resorption by giant-cell proliferation gives rise to a tumor of the tendon sheath. Whether the tumor is of tendon sheath or synovial origin the typical fibrocartilaginous structure of the sesamoid bone may be found remaining in the tumor.

92 Razemon, P, and Bizard, G. Les tumeurs primitives des articulations, *Rev de chir*, Paris **69** 229-266, 1931.

93 Bonn, R. Xanthom des Kniegelenks als Unfallfolge, *Arch f orthop u Unfall-Chir* **33** 146-148, 1933, abstracted, *Am J Cancer* **20** 777-778 (March) 1934.

94 Kling, D H and Sashin, D. Hemorrhagic Villous Synovitis of the Knee Joint Due to Xanthoma. Report of a Case, *Arch Surg* **30** 52-61 (July) 1930.

95 Geschickter C F, and Copeland, M M. Tumors of Bone (Including the Jaws and Joints), *Am J Cancer* **26** 747-752 1936.

Since the first tumor was reported in 1865, and covering a period of seventy-four years (to and including 1938), 43 lesions of the synovial membrane have been described in the literature, making an average appearance of approximately one tumor in two years.

Statistical Analysis—All the available literature since about 1850 has been reviewed, and it is felt that practically all the reported cases are referred to here. Complete data were not always available, but statistics have been compiled on a sufficient number of cases to enable one to arrive at certain definite conclusions. These tumors have heretofore masqueraded under so many names that at times it was difficult to decide to what group of pathologic entities they actually belonged. In some instances it was felt that certain ones belonged to the group of benign xanthomas in spite of the previously expressed opinions, and these tumors have been classified under the heading of probable xanthomas. When complete evidence was lacking as to their true nature or when the evidence pointed toward malignant or otherwise diverse characteristics, the growths were discarded. Of 36 doubtful lesions, 20 were of the latter class and had been diagnosed under such names as fusocellular, globocellular or fibrofusocellular sarcomas, fibromyxosarcomas or melanotic sarcomas. The duration of these tumors had been comparatively short, the growth had been fairly rapid, recurrence had been early or other such similar evidences of the presence of malignant changes not consistent with the true nature of xanthoma had been present.

In the cases collected from the literature there were 317 patients with 327 tumors, 274 had involvement of the tendon sheaths and 43 had involvement of the synovial membranes. Two hundred and sixty-nine patients with growths in the tendon sheaths had 1 tumor each, 3 patients had 2 tumors each, one patient had 3, and in 1 there were 6 tumors. Of the group with tumors of the synovial membranes each patient had involvement of only one joint.

The sex was recorded in 236 instances, 129 of the patients being women and 107 men, or 55 per cent women and 45 per cent men. In 220 instances the age and sex were both recorded, of this number 119, or 54 per cent, were women and 101, or 46 per cent, were men. In 3 cases the age but not the sex was reported, making a total of 223 in which the age was listed. The average age of the 119 women was 37.3 years, and that of the 101 men was 38 years. The average age for the entire group was 37.5 years. Arranged by decades, the largest group fell in the third, with 61, the fourth running second with 44. The oldest patient was a man 82 years old, reported by Malherbe,¹¹ the youngest a patient aged 5 years, of unspecified sex, recorded by Garrett.⁴³

In 156 cases the duration of the tumor was cited. One hundred and thirty-three tumors involved the tendon sheaths, with an average duration of five years and four months. Twenty-three involved the synovial membranes, with an average duration of three years and eleven months. For the entire group the average duration was five years and one month. The shortest duration was three weeks (the patient had a tumor on the tendon sheath of the right middle finger, the case was reported by Bessesen)⁵⁶. The longest was thirty-one years, recorded by Fritsch,¹¹ the patient having a growth involving a tendon sheath of the right foot.

The size of the tumor was recorded in 109 cases. This was not always the exact size in inches or centimeters, but a comparative one, from which an attempt was made to reconstruct the measurement as nearly as possible into centimeters. Of 66 tumors connected with the tendon sheaths of the upper extremity the average size was approximately 2 by 1 cm. In the lower extremity, involving the tendon sheaths, 27 tumors showed an average size of 5.5 by 4 cm. The average for both was 3 by 2 cm. Of 16 tumors of the synovial membranes the average size was 3.5 by 2.5 cm. The average size for the entire group was about 3 by 2 cm. The largest tumors were those located about the foot and ankle, two or three of these were as large as 9 by 7 cm. The smallest were those involving the fingers, the smallest of these was approximately 0.5 cm in diameter.

The records are not complete as to the presence or absence of trauma. Of the 327 cases studied, a definite record of injury could be found in only 61, or 19 per cent. Of this group, trauma was referred to 48 times in the cases of tumor of the tendon sheaths, or 17 per cent. In 13, or 30 per cent of cases of tumor involving the synovial membranes a definite history of previous trauma was obtained. Of the complete group of tumors reported, 166 had no connection with injury or absence of injury. Thus, since the presence or absence of trauma is not cited in over half of the cases, the aforementioned figures could be markedly altered in either direction if more complete information were available, and therefore it would appear that they are not of much real value from the statistical standpoint.

The occupation of the patients was stated in only a few instances.

The location of 62 of the 327 tumors was not recorded, leaving 265 for which definite positions were stated. One hundred and forty-one, or 53 per cent, involved the tendon sheaths of the fingers, of which 72, or 51 per cent, were located on the flexor surface. Thirty-four of these were on the right hand and 19 on the left, in 19 instances the extremity was not indicated. The extensor surface was involved 18 times (13 per cent), the tumor being on the right hand 11 times, on the left 5 times and on an unspecified finger twice. Of the remaining group, 39, or 28 per cent, were not given a definite position as to sur-

face, and in 12, or 9 per cent, the tumor was located on the medial surface, the lateral surface or a combination of these surfaces. Of the group that was not given a definite position as to surface 14 were on the right hand, 7 on the left, and in 18 the side was not indicated. In the miscellaneous group, the right side was involved 6 times and the left once, in 5 instances the side was not indicated. The index finger was the most common site, 37, or 26 per cent of the tumors occurring there. The right index finger was involved 19 times and the left 8 times, in 10 instances the side was not stated. The middle finger was next with 30 tumors, or 21 per cent. The right side was affected 18 times and the left 6 times, in 6 instances the side was not indicated. The rest of the fingers followed in order, the little finger showing the least incidence. Of the 141 tumors there was involvement of the fingers of the right hand in 65 and of those of the left in 32. In 44 instances the extremity was not designated.

It appears that the tumors were about equally distributed as to the level at which they occurred on the fingers. However, in most instances—in fact, in 86 of the 141, or 60 per cent—no level as to position in relation with the phalanges was given, thus it is impossible to arrive at any positive conclusion concerning this point.

Of the 81 remaining tumors of the tendon sheaths of which the position was known, 37 appeared about the foot and ankle, most often on the right side and on the extensor surface. Sixteen occurred on parts of the hand other than the fingers, 13 on the toes, 10 about the wrist, 3 on tendon sheaths about the knee, and 1 each on the leg and elbow. Of this group 30 occurred on the flexor surface, 23 on the extensor, 7 on the lateral, 6 on the medial, 1 on the medial and lateral, in 14 instances the surface was not recorded. Of the 222 tumors of known location involving the tendon sheaths, 102 were on the flexor surface, 41 on the extensor, 11 on the lateral, 9 on the medial, 4 on the flexor and extensor, and 1 on the medial and lateral, 1 included all surfaces, and in 53 instances the surface was not indicated. Of this group, 99 were on the right extremities and 56 on the left, in 67 instances the side was not indicated.

Of the 43 tumors of the synovial membranes 13 were diffuse and 26 were pedunculated. Thirty-seven involved the knee, 3 the ankle and 3 the tarsal articulations. Fourteen were on the right, and 18 on the left. In 11 instances the side was not mentioned.

In the entire group of tumors of both the synovial membrane and tendon sheath, the right side was involved 113 times and the left 74 times, in 78 instances the side was not indicated. One hundred and sixty-eight tumors were on the upper extremity, of which 76 were on the right side, and 41 on the left, in 51 instances the side was not speci-

fied Ninety-seven were on the lower extremity, involving the right side 37 times and the left 33 times, in 27 instances the side was not specified

Of the 327 tumors reported in the literature, a record of treatment was observed for 243 tumors of the tendon sheaths and for 35 tumors of the synovial membranes, making a total of 278 tumors treated Local excision was done for 229 tumors of the tendon sheaths, excision and cautery for 2, excision and roentgen therapy for 1, and amputation for 11 Of the tumors of the synovial membrane, local excision was completed for 24, local excision plus roentgen therapy for 2, synovectomy for 6 and partial synovectomy for 3

A record of a follow-up was found in only 153 instances, recurrence was reported in 25, or 16 per cent Among 18 tumors of the synovial membrane there were 5 recurrences and of 135 tumors of the tendon sheaths, 20 recurred

A record of the values for blood cholesterol was found in only a very few of the cases Mason and Woolston⁴⁹ reported the cholesterol content of the blood in 3 cases, with readings of 96 mg, 98 mg and 131 mg per hundred cubic centimeters in the first, 165 mg and 143 mg in the second, and 185.3 mg in the third Ragins¹⁰ reported the results of chemical examination of the blood in both of his cases The concentration of cholesterol was 147 mg per hundred cubic centimeters of blood in the first and 177 mg in the second Gorog⁵⁰ reported a value for blood cholesterol of 131 mg per hundred cubic centimeters in his only case Zumtobel⁷⁰ reported the value for cholesterol in all 4 of his cases, these values were 180 mg, 130 mg, 245 mg, and 280 mg per hundred cubic centimeters respectively Thannhauser and Magendantz⁷³ found the value for blood cholesterol to be 200 mg and that for cholesterol esters 160 mg, with a value for total cholesterol of 360 mg, in their first case In the second the value for cholesterol was 107 mg, that for cholesterol esters 103 mg and that for total cholesterol 210 mg These authors were the only ones to report a chemical analysis of any of the tumors, the report for the first case was total cholesterol, 9 mg, and total phosphatides, 11 mg per hundred cubic centimeters Thus, only twelve reports of chemical study of the blood could be found in the literature

MATERIAL OF PRESENT STUDY

Since 1919, 70 patients have presented themselves at the Mayo Clinic with one or more xanthomas of the extremities involving tendon sheaths or synovial membranes (table 1) Of this group 50, or 71 per cent, were women and 20, or 29 per cent were men The average age of the women was 45 years, and that of the men 43 years The average age of the entire series was 44 A man and a woman aged 68 were the oldest patients a boy of 16 was the youngest Twenty-two

TABLE 1—*Xanthoma of Tendon Sheaths and Synovial Membranes*

Case	Sex	Age	Duration	Size	Trauma	Infection	Location	Treatment	Result
1	M	48	2 years	1 1/2 by 1 cm		Yes	Proximal phalanx of left middle finger	Local excision	No recurrence
2	F	60	Several years	1.5 cm, 1 cm		Yes	Proximal phalanx and distal phalanx of right index finger	Local excision and roentgen therapy	Two subsequent excisions, 4 and 6 months later recur
3	F	61	1 1/2 years	3 by 1 by 1 cm		No	Fourth flexor tendon sheath of palm of right hand	Local excision	No recurrence
4	M	42	3 years	1.5 by 0.5 cm	Yes	No	Proximal phalanx (flexor surface) of right ring finger	Local excision	No recurrence
5	M	49	3 years	1 by 0.5 cm	Yes	No	Distal phalanx of left little finger	Local excision	No recurrence
6	M	47	5 years	1 by 1 cm	No	No	Proximal phalanx (lateral surface) of right middle finger	Local excision	No recurrence
7	F	49	6 years	12 by 12 mm	No	No	Distal phalanx (flexor surface) of right little finger	Local excision	No recurrence
8	M	63	Several years	1 by 1 cm	No	No	Proximal phalanx (lateral surface) of left index finger	Local excision	No recurrence
9	F	67	2 1/2 years	2 by 1 cm	Yes	No	Middle phalanx (flexor surface) of left middle finger	Local excision	Died ?
10	M	21	3 months	3 by 1 cm	No	No	Middle phalanx (flexor surface) of left middle finger	Local excision	No recurrence
11	M	13	1 year	1 by 1.5 cm	No	No	Flexor surface, interphalangeal joint, of right thumb	Local excision	No recurrence
12	F	38	3 years	1 by 1.5 cm	Yes	No	Extensor surface of distal joint of right middle finger	Local excision	No recurrence
13	M	53	6 years	13 by 0 by 5 cm		No	Tendon sheaths of right internal and external ham strings	Local excision and roentgen therapy	Second excision here 3 months later died
14	M	52	6 years		Yes	Yes	Right ring finger	Local excision	No recurrence
15	M	56				No	Right posterior tibial and peroneal tendon sheaths and sole of foot	Local excision and roentgen therapy	Recurred 3 1/2 mo later unknown result after 2d excision
16	M	53	3 years	2.5 by 2.5 cm	No	No	Flexor surface of interphalangeal joint of right thumb	Local excision	Recurred
17	F	43	4 months	7 by 7 mm	Yes	No	Extensor surface of distal joint of left ring finger	Local excision and roentgen therapy	No recurrence
18	M	63	23 years	2.5 by 1.5 cm	Yes	No	Extensor surface of proximal phalanx of left middle finger	Local excision	No recurrence
19	F	42		18 by 11 mm	Yes	No	Flexor surface of distal phalanx of right little finger	Local excision	Recurred
20	F	31	2 years	3 by 2 cm	Yes	No	Left anterior tibial tendon sheath	Local excision and roentgen therapy	No recurrence
21	F	52	2 years	1.5 by 1.5 cm	Yes	No	Extensor surface of distal phalanx of left index finger	Local excision	No recurrence
22	F	40	12 years	22 by 18 cm	Yes	No	Suprapatellar pouch of left knee	Excision of supra patellar pouch	No recurrence
23	M	40	1 month	1.5 by 1.5 cm	No	No	Flexor surface of distal phalanx of right thumb	Local excision	No recurrence
24	M	43	1 year	1 by 1 cm	Yes	No	Extensor surface of distal phalanx of left index finger (recurrent)	Local excision	No recurrence

2.	F	J3	12 years	2.5 by 2.5 cm 2 by 2 cm 1 by 1 cm	Yes	Two tumors left knee	Local excision	?
25	I	62	1 year		No	Flexor surface of middle phalanx of right middle finger	Local excision	No recurrence
27	I	61		1.5 by 1 by 0.5 cm	No	Flexor surface of distal phalanx of right middle finger	Local excision	?
28	F	52	10 years	2.5 by 1.5 by 1 cm	Yes	Flexor surface of distal phalanx of left middle finger	Local excision	No recurrence
29	I	20	8 years	2.5 by 2 by 1 cm	Yes	Flexor surface of distal phalanx of right thumb (recurrent)	Local excision	No recurrence
30	I	51	2 years	2 by 2 cm	No	Distal joint of left middle finger	Local excision	?
31	M	26	25 years	7 by 5 by 3 cm	No	Tendon sheaths (anterior surface) of right ankle	Local excision and roentgen therapy	No recurrence
32	I	50	10 years	1 by 1 cm 6 by 6 mm	Yes	Flexor and extensor surfaces of distal phalanx of right index finger	Local excision	Appearance on other fingers
33	I	37	7 years	1.5 by 1.5 cm	No	Flexor surface of middle phalanx of right middle finger	Local excision	No recurrence
34	I	63	18 months	1 by 1 cm	No	Distal joint of left little finger (recurrent)	Local excision	No recurrence
35	I	47	10 years	3 by 2 cm	No	Flexor and extensor surfaces of middle phalanx of right middle finger	Local excision	No recurrence
36	M	30	3 years	4 by 4 mm	Yes	Extensor surface of middle phalanx of right ring finger (recurrent)	Local excision	Recurred
37	F	42	2 months	1 by 0.5 cm	No	Extensor surface of proximal phalanx of right middle finger	Local excision	No recurrence
38	I	49	5 years	7 by 7 mm	Yes	Extensor and medial surfaces of distal phalanx of right middle finger	Local excision	Recurred 1 year later 2d excision too recent
39	M	16	2 years	18 by 15 by 13 mm	No	Extensor surface over right 5th metacarpal head	Local excision	No recurrence
40	I	20	15 years		No	Right peroneal tendon (recurrent)	Local excision at home roentgen therapy	No recurrence
41	M	43	7 years	1 by 1 cm	No	Extensor surface of middle phalanx of right ring finger	Local excision	No recurrence
42	M	63	5 years	2 by 2 cm	No	Flexor surface of middle phalanx of right middle finger	Local excision	Appearance of 2 tumors in right palm
43	I	37	10 years	2 by 1 cm	No	Middle phalanx of left index finger	Local excision	No recurrence
44	M	50		1.5 by 1.2 by 0.9 cm	Yes	Flexor surface of proximal phalanx of right little finger	Local excision	No recurrence
45	I	28	2 years	1 by 1 cm	Yes	Right palm	Local excision	No recurrence
46	I	24	19 years		Yes	Extensor surface of middle joint of right middle finger	Local excision	No recurrence
47	I	33	1 year	1.5 by 1 cm	No	Proximal phalanx of right ring finger	Local excision	Recurred
48	M	37	18 months	2 by 2 cm	Yes	Extensor surface of interphalangeal joint of right great toe	Local excision	?
49	I	40	3 years	1.5 by 1.5 cm	No	Extensor surface of interphalangeal joint of right little toe	Local excision	No recurrence
50	M	43	1 year	0.5 by 0.5 cm	Yes	Flexor and extensor surfaces of distal phalanx of right middle finger	Local excision and roentgen therapy	?
51	M	19	3 years	1 by 1 cm	No	Extensor surface of interphalangeal joint of left thumb	Local excision	No recurrence
					No	Synovia of right knee	Local excision	No recurrence after 5 months

TABLE 1—*Xanthoma of Tendon Sheaths and Synovial Membranes—Continued*

Case	Sex	Age	Duration	Size	Trauma	Infection	Location	Treatment	Result
52	F	40	4 years	7 by 7 mm 7 by 7 mm	?	No	Flexor surface of proximal phalanx of right middle finger, flexor tendon sheath of right middle finger, palm of hand	Local excision	No recurrence after 4 months
53	F	20	1 year	6 by 4 by 1.5 cm	No	No	Synovia of left knee	Local excision	No recurrence
54	F	59	1 month	2.5 by 1.5 by 1 cm	Yes	Yes	Flexor surface of distal phalanx of right index finger	Local excision	No recurrence
55	M	28	7 years	3 by 2 cm	Yes	No	Left quadriceps tendon	Local excision	No recurrence
56	F	60		1 by 1 cm	No	No	Proximal phalanx of left index finger	Local excision	Apparently no recurrence
57	F	52	2 years	5 by 3 by 2.5 cm	Yes	No	Right peroneal tendon sheaths, erosion of fibula	Local excision	No recurrence after 6 weeks
58	F	34	6 months	1 by 0.7 cm		No	Lateral surface of distal joint of right little finger	Local excision	Recurred 4 months later no recurrence after second excision
59	F	38	10 years			No	Dorsum of right foot	Local excision	No recurrence
60	F	47	2 years	1 by 1 cm	Yes	Yes	Lateral surface of proximal phalanx of right middle finger	Local excision	No recurrence
61	M	27	3 years	0.5 by 0.5 cm	Yes	No	Extensor surface of middle joint of right little finger	Local excision	No recurrence
62	F	28	7 years		Yes	No	Dorsum of right foot and ankle (recurrent)	Local partial excision and roentgen therapy	Still present
63	F	79	10 years	3 by 3 cm	No	No	Both Achilles tendons, medial aspect of distal phalanx of right index finger lateral aspect of proximal phalanx of right middle finger medial aspect of proximal phalanx of both thumbs	Local excision	?
64	F	42	23 years	3 by 2 cm	No	No	Both Achilles tendons, left plantar fascia	Local excision	
65	F	41	6 years	1 by 1 cm largest	No	Yes	Right Achilles tendon distal phalanx of right index of right thumb	Local excision	Died of septal carcinoma
66	F	40	15 years	5 by 3 cm 1 by 1 cm 2 by 2 cm	No	Yes	Both Achilles tendons right and left extensor tendon sheaths over third metacarpal bone both triceps tendon sheaths	Local excision roentgen therapy from Achilles tendons and fingers	No recurrence
67	M	15	1 year	2.5 by 2.5 cm	Yes	No	Tendon sheath at insertion on right radius erosion of radius	Local excision	No recurrence 1 year after
68	F	68	6 months	7 by 2 cm	No	No	Dorsum of left wrist	Local excision	No recurrence
69	F	52	1 year	1.5 by 1.5 cm	Yes	Yes	Extensor surface of distal joint of right ring finger	Local excision	No recurrence
70	F	10	20 years	1.1 by 8 cm	Yes	No	Diffuse synovial membrane of right knee	Synovectomy and roentgen therapy	No recurrence after 2 1/2 mos

fell in the fifth decade, the sixth decade was next with 14, the fourth followed with 12, there were 10 in the third, 9 in the seventh and 3 in the second. None were in the first decade.

The occupation of 69 of the 70 patients was recorded. Thirty-nine were housewives, who are notorious for minor accidents and injuries that frequently go unnoticed and untreated. The remaining 30 were engaged in various occupations, ranging from sedentary clerks to farmers, laborers in steel and other persons in hazardous positions. Practically all were engaged in vocations that more or less constantly exposed them to the dangers of everyday mild to severe trauma, from the constant pressure of a pencil against the fingers in writing to the handling of heavy and complicated machinery, the havoc of which is seen every day in the dispensaries and outpatient departments.

The weight of each patient was determined. It was found that in 37, or 53 per cent of cases, there was a record of obesity, with an average of about 24 pounds (10.9 kg) overweight per patient.

Thirty-one, or 44 per cent, of the patients had a specific history of trauma, 14, or 20 per cent, had arthritis in the involved extremity, and 6 had a history of both infection and trauma, making a total of 39, or 56 per cent, with either an infectious or a traumatic background.

In 62 cases there was a record of the duration of the tumor, the average being six years and one month. The longest duration was twenty-eight years, there were 2 patients, 1 of whom had a tumor of the left middle finger and 1 who had xanthomas of the right and left achilles tendons and the left plantar fascia. The shortest duration was one month, the growth was a tumor of the right middle finger.

In 70 patients observed there were 88 tumors. Sixty-five patients had 82 tumors of the tendon sheaths, and 5 had 6 tumors of the synovial membranes. There were 4 patients with 2 tumors each and 2 with 3 tumors each. Two patients had 6 each. Sixty-four of these lesions were located on the upper extremity and 24 on the lower. Of those occurring on the upper extremity, 54 were on the fingers, 6 on the hands, 3 about the elbow and 1 on the wrist. In the lower extremity, 15 were located in the tendon sheaths about the foot and ankle, 2 about the knee, 1 on a toe and 6 in the synovial membrane of the knee. Sixty were on the right side and 28 on the left. The flexor surface was involved 28 times, the extensor 37 times, the medial 3 times, the lateral 4 times and the flexor and extensor twice. In 8 instances the surface was not indicated. Thirty-eight of the tumors involving the tendon sheaths of the fingers were on the right extremity, and 16 were on the left, 20 occurred on the flexor surface, 17 on the extensor, 4 on the lateral, 3 on the medial and 2 on the flexor and extensor. In 8 instances the surface was not indicated. The middle finger was the most common site with 19

tumors, the index was next with 12, and this was followed by the thumb and ring fingers with 8 each and by the little finger with 7. In 17 instances the tumor was situated on a level with the distal phalanx, in 15 it was opposite the proximal phalanx, in 9 it was opposite the middle phalanx, in 6 it was over the distal joint, in 5 it was over the middle interphalangeal joint, and in 1 the level was not recorded. The remaining tumors of the tendon sheaths were located as has been described.

The tumors of the synovial membrane were found in the knee, and only 1 was a real diffuse xanthoma. One was diffuse but limited to the suprapatellar pouch, and the remaining 4 were pedunculated. The right knee was involved twice, with 2 tumors, the left 3 times, with 4 tumors.

Twelve of the patients on their first visit to the clinic presented a recurrent tumor. In 10 there had been only one recurrence, in 2 there had been two recurrences. The previous operation had been done from six days to eleven years before the patient arrived here. In 7 patients the interval between operation and recurrence was known, the average approximating one year.

The history elicited was usually the same, the patients complaining of a slowly growing, painless mass, seldom causing any disability except when the size was sufficient to produce mechanical block of the motion of a joint. In some instances it was preceded by injury, but often no history of a definite injury could be elicited. Frequently the patient came for operation with the fear of a malignant lesion as his prime reason, in other instances treatment was sought only for cosmetic purposes. The fear of a malignant lesion in most cases was due to suspicions raised by the patient's family physician. In some cases biopsy had been done, with the usual diagnosis of sarcoma, and the physician had advised the patient to have the extremity amputated.

On physical examination the usual picture was that of a subcutaneous firm mass of varying size and shape, not tender on pressure and located in the vicinity of the tendon sheaths or on them (fig 1). The overlying skin was unattached, but evidence of attachment to deeper structures was present. Even if it was evident that the mass was fastened to the sheath, motion of the tendon in the sheath was not hampered. There was never any ulceration of the skin or sign of local or general metastasis, and in only 1 case was there a record of local heat, this occurred in a tumor of the ankle seen during the past year that had been previously operated on and had received much local treatment subsequently. The signs and symptoms observed in the knee were those of any internal derangement of this joint.

The results of routine laboratory tests were all essentially negative with regard to this condition. In 12 cases the values for total blood lipoids were determined. In 10 of these the values for blood cholesterol

cholesterol esters, lecithin and total fatty acids were also determined, and in 2 the values for cholesterol esters and lecithin were not recorded. In 1 case of the 10 a second determination was carried out after two months of a cholesterol-free diet. The normal for these substances as determined at the Mayo Clinic is given in table 2. Using the ratio of the mean normal value of cholesterol and cholesterol esters as a standard (14), we determined the ratio of these values for each patient to see whether there was any variation. In 6 patients there was an absolute elevation of the value for total blood lipoids. In 10 cases the ratio of cholesterol to cholesterol esters was determined, in 5 there was an increase in the ratio and in 3 a decrease, and in 2 the ratio was normal.

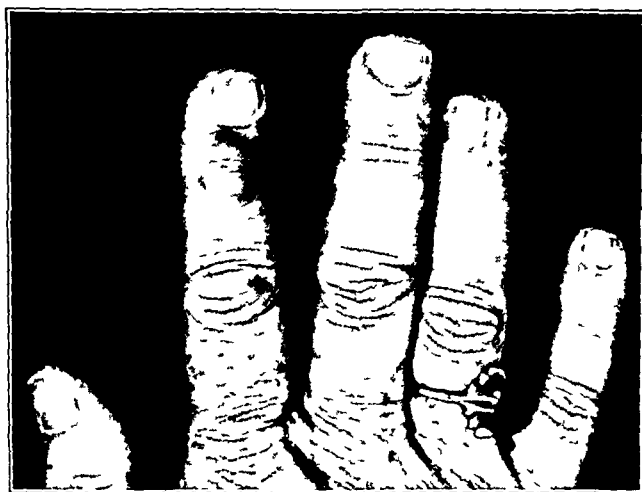


Fig 1—Xanthoma involving the extensor tendon sheath of the right index finger

In all but 2 cases, then, there was either an elevation of the absolute values or a disturbance in the cholesterol-cholesterol ester ratio. It is interesting to note in the case of the patient who had been on a cholesterol-free diet that although the absolute values had returned to normal the ratio of cholesterol to cholesterol esters remained the same (table 2).

Sixty-nine of the 70 patients were treated surgically at the Mayo Clinic. One patient came here after operation had been completed at home bringing with him the tissue that had been excised. After the diagnosis had been established, the patient was given a course of roentgen treatment. Sixty-seven patients were treated by local excision alone and 8 were given roentgen treatment in addition to local excision. This was done only when it was felt that all of the tumor had not been

or could not be completely removed. In 1 case of diffuse xanthoma of the knee, a synovectomy was done. In 9 a recurrence is known to have taken place, and in 5 of these a second excision was carried out, in 1 of these the patient received, in addition, a course of roentgen treatment.

Most of the tumors were easily shelled out intact and without much damage to the surrounding tissues. In some instances (for example, case 62) in which the tumor was diffuse and infiltrating, complete removal was not possible, and in case 66 a marked involvement of the achilles tendons made it necessary to do a secondary plastic operation on the tendons. In nearly all cases excision was carried out with the region under local anesthesia and with a tourniquet.

TABLE 2—*Blood Chemistry of Patients with Xanthoma*

Date	Case	Cholesterol	Cholesterol Ester	O CE Ratio	Leecithin	Total Fatty Acids	Total Lipoid
Normal		160-200 Mg /100 cc	110-145 Mg /100 cc	1.38-1.45	200-250 Mg /100 cc	33.3-30 Mg /100 cc	60-50 Mg /100 cc
Mean		180	127.5	1.41	225	34.5	25
6/27/38	38	321	208	1.54	278	368	63
2/ 1/38	49	175	136	1.29	200	265	440
6/ 4/38	51	126	89	1.42	172	251	347
6/20/38	52	168	100	1.68	208	211	349
1/18/38	55	139	116	1.20	192	242	381
6/21/38	58	238	181	1.31	218	372	610
6/ 7/38	59	333	214	1.56	315	363	606
6/20/38	62	231	141	1.64	198	289	20
8/ 9/38	62	170	104	1.63	185	247	41
3/ 2/38	65	206	132	1.56	208	394	600
3/19/38	66	476				540	1016
4/26/38	67	222				306	25
7/26/38	69	248	174	1.43	250	495	43

The size of the excised tumors was determined in 74 instances. Of 56 tumors of the upper extremity the average size was 1.5 by 1 cm. Of 18 tumors involving the lower extremity the average size was 5.5 by 4 cm. The average size for the entire group was 2.5 by 2 cm.

Grossly these tumors appeared as round or ovoid, practically always lobulated, well encapsulated solid masses, moderately firm to quite firm varying from grayish yellow through yellowish brown to reddish brown. A tumor might show all these colors, or it might show only one. Some, particularly those about the ankle, showed no limiting capsule, and some were of a rather infiltrating nature. This, however, was the exception and not the rule. They cut with increased resistance depending on the relative amount of fibrous tissue, cellular tissue and fat. The cut surface revealed the same varieties of color as did the outer surface, and in addition each lobule was outlined by whitish strands of fibrous tissue extending inward from the capsule in an interlacing manner (fig 2).

Microscopically, their appearance varied (fig 3). Certain definite characteristics, however, were nearly always observed, for example, foam cells, foreign body giant cells, pigment and fat. The cellular and fibrous elements were always the same, but in some the fibrous tissue predominated and in others the cellular constituents were foremost.



Fig 2—Gross appearance of a diffuse xanthoma removed from the suprapatellar pouch

In some the fibrous elements were predominant in one section, and in the next the cellular elements might make up the greater part of the section. The fibrous tissue varied from fine strands of tissue to heavier and denser portions. In some an osteoid-appearing tissue was present but closer examination revealed very dense fibrous tissue.

The type cell of the stroma was in all instances the same (fig 4). It was polyhedral, oval or round, containing one nucleus that was

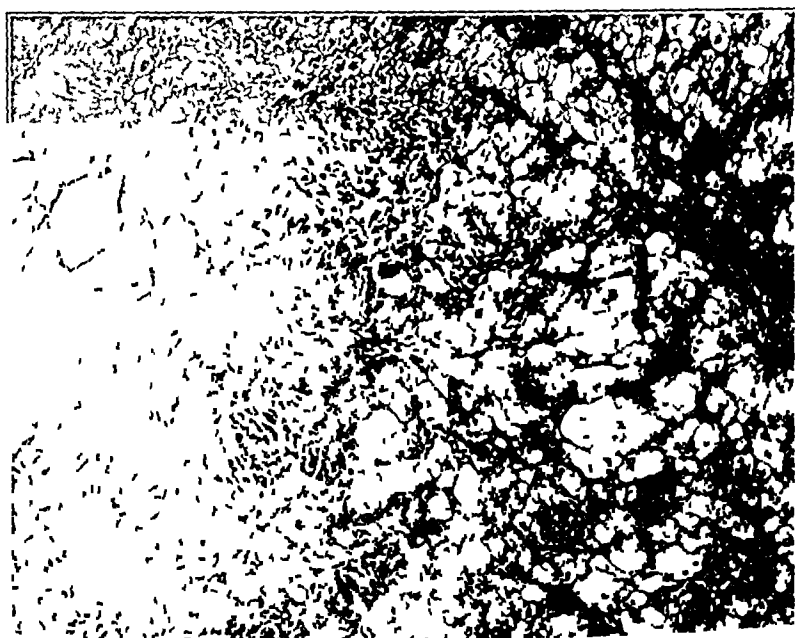


Fig 3—Xanthoma showing large numbers of foam cells in the right side of section and cholesterol clefts in the left side. Fibrous and cellular stroma and several foreign body giant cells are present. $\times 60$



Fig 4—Xanthoma, showing the shape and structure of a foreign body giant cell, with characteristic cytoplasm and many endothelium-like nuclei. The surrounding tissue shows typical endothelium-like stroma cells with their pale staining nuclei and prominent nucleoli. $\times 440$

usually large and either round or oval. Each nucleus stained lightly and contained one and sometimes two darkly stained nucleoli. The cytoplasm of these cells took the eosin stain faintly and was rather homogeneous and slightly granular. These cells looked not unlike endothelial cells and were arranged usually in solid masses, separated only by the interlacing strands of fibrous tissue. Some spindle cells were present in small numbers, and very few polymorphonuclear leukocytes were observed in any one section. Mitotic figures were seen only on rare occasions and in only 12 of the tumors. The type cell did not show the polymorphism, polychromatophilia or atypical mitosis characteristic of malignant tissue. No tumor giant cells were found in any one section.

Foam cells were found in all but 8 tumors (fig 3). These cells were of varying size and shape, their cytoplasm had a granular, foamy appearance, and the nuclei were smaller than those of the type cell, having a shrunken pyknotic appearance. There rarely was more than one nucleus, and it took a heavier stain than did the type cell. The foam cells were found in varying amounts, from tiny groups to collections so large that they made up practically the entire cellular content of the tumor. In some sections they were seen only on the periphery, in others they were scattered throughout the tumor.

Giant cells of the foreign body type were found in all but 1 (fig 4). They varied in size and shape, but a rectangular cell seemed to predominate. Their nuclear content varied from two or three per cell up to two hundred or more. These cells were found in large numbers in close approximation to hemorrhagic regions, pigment and regions showing cholesterol crystals. They were numerous in some sections, showing as many as fifty-two per low power field. In some sections only a few could be found in the entire lesion. Their cytoplasm was pink and homogeneous, with nuclei that resembled those of the cells of the stroma, in other words, they looked like endothelial cells. Each giant cell was usually seen lying in a clear space, but in some cases they were in direct apposition to the stroma of the tumor.

In all the sections except one the presence of hemosiderin pigment was revealed by the iron stain method. The pigment content varied from small amounts to amounts sufficient to fill the section heavily throughout. It was chiefly intracellular, the stroma cells in many instances revealed large deposits. Innumerable giant cells displayed intracellular pigment, and in nearly every section in which foam cells were present, from a few to the entire group, intracellular pigment was seen, and in some these cells were heavily laden with pigment (fig 5).

Every section studied displayed the presence of fat when stained by the scarlet red method. The fat varied from very small amounts to amounts sufficient to load the section. It too was chiefly intracellular, and the largest amounts, of course, were within the foam cells. Some of the foreign body giant cells also showed some intracellular fat. Twenty-eight tumors displayed cholesterol crystals, seen principally in the foam cells (fig 6). Ten tumors showed cholesterol clefts. Four sections showed both crystals and clefts, thus 34, or practically 50 per cent, revealed the presence of either cholesterol crystals or their clefts.

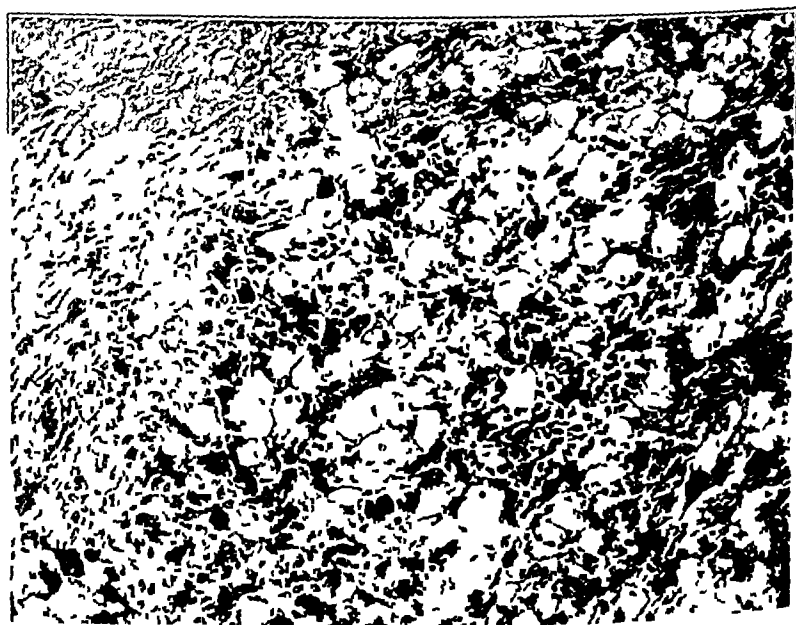


Fig 5—Xanthoma, showing the pigment content of the foam cells and the larger deposits in the stroma cells. $\times 200$

There was evidence of a good blood supply in all the tumors. Of course this varied a great deal, but in every one small blood vessels could be found about the periphery, and in some larger vessels were visualized. In a large number, in addition to the peripherally arranged vessels, numerous small blood vessels and sinuses were distributed throughout. Innumerable sections showed scattered hemorrhagic regions.

An attempt was made to grade these tumors according to their relative cellular and fibrous content, foam cell content, giant cell content, fat content and pigment content. A tumor was called grade 4 if it showed more than 75 per cent cells or more than 75 per cent fibrinous tissue, for example, grade 4 cellular. If the cellular or fibrous content made up 50 to 75 per cent the tumor was designated

as grade 3. Of course if a tumor is grade 3 cellular, it must be grade 1 fibrous and vice versa. When the tumor consisted of equal parts of cells and fibrous tissue it was called grade 2 fibrous and cellular. The tumors were graded also on a basis of percentage of foam cells, grade 1 being a tumor made up of 1 to 25 per cent foam cells, grade 2, 25 to 50 per cent, grade 3, 50 to 75 per cent, and grade 4, 75 to 100 per cent. They were graded as to fat content on a similar rating. The grade according to content of foreign body giant cells was figured on the following basis. Tumors in which there appeared only a few of these cells were designated as grade 1, those showing one to seventeen per low power field as grade 2, those with eighteen to thirty-five



Fig 6—Xanthoma, showing foam cells containing intracellular fat and cholesterol crystals. Scarlet red stain, $\times 200$

per low power field, as grade 3, and those in which thirty-six to fifty-two per lower power field were seen, as grade 4. Grading according to the pigment content was decided by the following method. Sections showing small isolated amounts up to small amounts of pigment scattered throughout were designated as grade 1, sections showing small to moderate amounts scattered throughout, as grade 2, sections with moderate amounts throughout, as grade 3, and sections with large amounts throughout, as grade 4.

A summary of these gradings is given in table 3 and is self explanatory. Sixty-eight tumors were thus examined histologically and

graded, 5 of them being recurrent lesions. It is of interest to note that the recurrent tumors usually showed the same relative amounts of the various constituents as had the original tumor.

A chemical analysis of these tumors was possible in only 3 cases (table 4).

Follow-up studies were obtained on 61 patients. In 9 instances no record of the result was obtainable, in 7 of these treatment had been recent, and the interval since operation was too short to make the results of any value at this time. One patient died of septicemia after operation. In the entire group there were 9 recurrences, a total of 12 per cent. In 3 patients, although there was no recurrence at the site

TABLE 3—*Summary of Constituents of Xanthomas*

Constituents	Absent	Grade 1	Grade 2	Grade 3	Grade 4	No Slide	Total
Cells				16	18	0	
Fibrous tissue				17	5	0	
Cells and fibrous tissue			12			0	68
Foam cells	8	40	9	5	6	0	68
Foreign body giant cells	1	13	45	6	3	0	68
Pigment	1	26	27	7	6	1	68
Fat		42	9	5	7	0	68

TABLE 4—*Percentage Lipoid Content of Xanthomas*

Case	Cholesterol	Cholesterol Ester	Lecithin	Total Fatty Acids	Total Lipoid
38					2.57
51	3.0	2.6	2.9	4.0	7.0
69	0.66		0.86	1.74	2.4

of the previous operation, similar tumors appeared at other sites, and in all instances these new appearances took place on the fingers and on the palm.

REPORT OF CASES

A report of a few cases illustrating most of the typical findings in this class of tumor will now be presented.

CASE 32—A housewife aged 50 was admitted to the Mayo Clinic on Sept. 4, 1933, complaining of a mass on the end of the right index finger of sixteen years' duration. Her family history and past medical history were irrelevant. The laboratory findings were essentially normal. The patient stated that the present tumor had appeared shortly after the finger had been caught in an electric wringer. Growth had been slow, and the tumor was painless and caused her no disability. On examination two firm, oval masses, the larger located on the extensor surface and the smaller on the flexor surface of the index finger, were found. Both were limited to the distal phalanx. There was no tenderness or local heat, and motion of the joint was not limited. On September 7 two growths were excised, a tumor

1 cm in diameter, from the extensor surface, and a tumor 6 mm in diameter, from the flexor surface. A letter received from the patient in September 1938 stated that there had been no recurrence of the tumor at the site of the previous operation but that similar masses had appeared on other fingers.

CASE 38—A nun aged 49 was admitted to the Mayo Clinic on July 15, 1935, complaining of a painless mass on the end of the right middle finger. The family history and past medical history were irrelevant. The results of routine laboratory tests were negative. The patient related that at the age of 15 she had pinched the end of this finger severely in a pump handle. Five years before admission a small mass had appeared in this region and had since been slowly increasing in size. The patient was curious concerning the nature of this growth and for this reason and cosmetic reasons wished to have it removed. On examination a small, firm mass about the size of a pea was found on the extensor surface of the distal phalanx of the right middle finger, toward the ulnar side. There was no tenderness, local heat or interference with motion of the joint or of the tendon. On July 19 a round, yellowish, firm tumor 7 mm in diameter was excised. The wound healed by primary intention, and the patient was dismissed.

On June 21, 1938, this patient returned with a similar mass at the site of the previous excision, which she stated had made its appearance about one year after the operation. There was some pain. The patient said that the tumor had been growing slowly. She stated that she was accustomed to doing a moderate amount of sewing, that she wore a thimble on this finger and that the thimble possibly irritated this region. The physical findings were similar to those recorded on her first visit. The values for blood lipoid were determined, that for cholesterol was 321 mg, that for cholesterol ester 208 mg, that for lecithin 278 mg, that for total fatty acids 368 mg and that for total lipoids 689 mg per hundred cubic centimeters of plasma. The cholesterol-cholesterol ester ratio was 1.54:1. On June 27 a second excision of a similar tumor was performed (fig. 7). The wound healed quickly, and the patient was put on a low cholesterol diet and dismissed. No further record of this patient has been available.

CASE 15—A farmer aged 56 came to the Mayo Clinic on Dec. 4, 1923, complaining of swelling, stiffness, soreness and a burning sensation of the right ankle. His past medical history was irrelevant. He said that his mother had had a similar mass for forty years. He stated that thirty-five years previously his right foot and ankle had been caught between two logs and severely bruised. There were pain and discoloration of the foot and ankle for one month, but no more trouble until six years previously, when he noticed that this ankle was larger than the other. There was no pain or tenderness at this time, and function was not impaired. The ankle slowly increased in size and became progressively weaker, he noticed the weakness particularly after too much use. After prolonged rest and in the morning it was stiff and sore, and recently a burning sensation had appeared in the overlying skin. On examination a fairly firm soft tissue mass of moderate size was found over the medial and lateral surface of the ankle, and this appeared to be connected posteriorly to the posterior tibial tendon. There was only slight tenderness, and there was no local heat. On December 14 the tumor was excised. It originated apparently from the posterior tibial tendon behind the internal malleolus and extended behind the tendons and nerves to the fibula, causing the achilles tendon to bulge for about 8 to 9 inches (20 to 22 cm). It involved the plantar structures, extending well down into the ball of the foot, and spread over the external malleolus,

forming a tumor here connected with the peroneal tendons. The posterior tibial nerve was completely surrounded by the tumor mass and had to be dissected free. The tumor was removed en masse (fig 8). There were no postoperative complications and convalescence was uneventful. The patient was dismissed in good condition.

On Oct. 24, 1927, he returned, stating that three and one-half months previously a mass had appeared over the external malleolus and had grown slowly toward the heel. A smaller mass had appeared behind the internal malleolus. He stated that he had sharp pain in the ankle at night after overuse. On examination a mass was palpable over the external malleolus and a smaller one posterior to the internal malleolus. There was limitation of motion of the ankle in all directions. On October 28 a second operation was performed. At this time the tumor was found

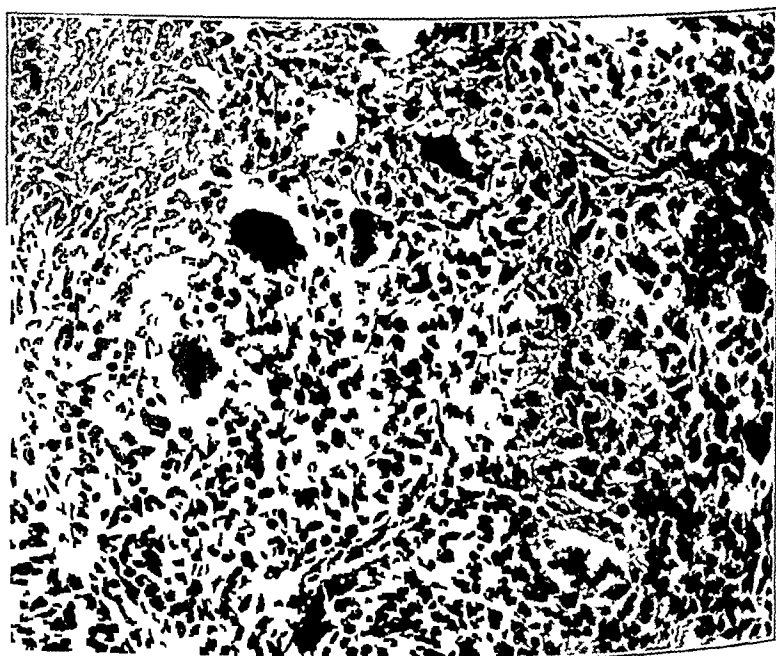


Fig 7 (case 38)—Xanthoma of the tendon sheath of the finger, showing the interlacing strands of fibrous tissue separating the typical endothelium like stroma cells and several foreign body giant cells. $\times 200$

to have extended into and destroyed the tibiotarsal joint capsule on its anterior and lateral aspects and had extended up the peroneal tendons and across the front of and up along the inner side of the foot. It was impossible to excise the tumor completely. On November 11 and December 2 roentgen treatments were given. Convalescence was uneventful, and the patient was dismissed. A letter received from him in June 1928 described some pain and swelling of the ankle but did not say whether the growth was increasing. No further word has been received.

CASE 51—A student aged 19 was admitted to the Mayo Clinic on May 31, 1932, complaining of a painful knee on weight bearing. His past medical and family history were irrelevant. He stated that three years previously he had twisted

knee several times while playing football and that during the past two years he had had attacks of pain in the knee after any twisting of the joint and on kneeling. There was no locking. A cast had been applied four weeks prior to admission and was still on when he arrived here. On physical examination there was grade 1 atrophy of the quadriceps muscle on a basis of 1 to 4. Flexion was limited to 80 degrees, there was no instability, and on the medial border of the patella a loose body could be palpated and rolled under the finger. The concentration of blood lipids at this time was as follows: cholesterol, 126 mg, cholesterol ester, 89 mg, lecithin 172 mg, total fatty acids, 251 mg, and total lipoids, 377 mg per hundred cubic centimeters of plasma. The cholesterol-cholesterol ester ratio was 1.41:1.

On June 4 the right knee was explored. When the synovial membrane was opened the palpable nodule which was about the size of a lima bean was found

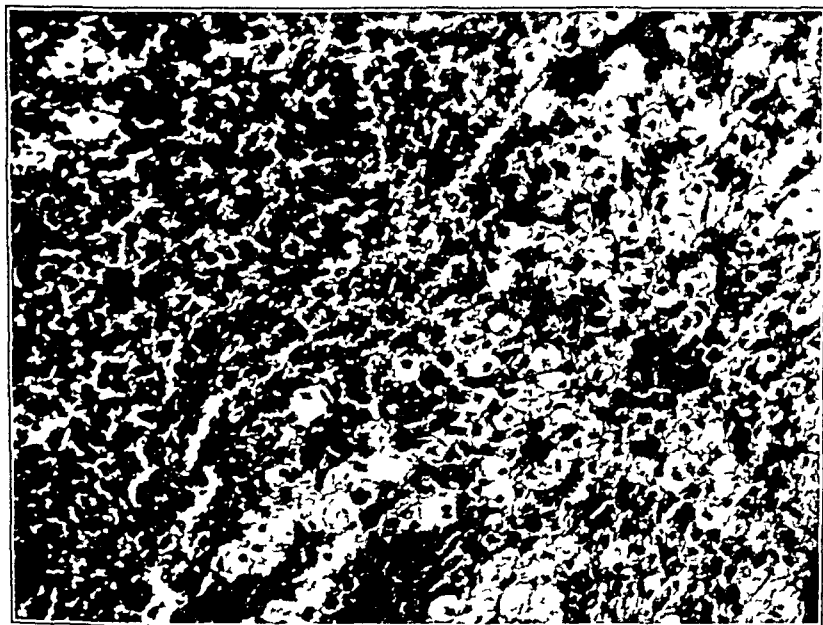


Fig 8 (case 15)—Xanthoma of the ankle, showing the typical cell and foam cells $\times 200$

attached to the synovial membrane on the medial side and hanging into the joint space. Osteochondritis dissecans of the medial condyle of the femur was present. The semilunar cartilages were not involved. The synovial membrane was somewhat thickened, and there were numerous small yellowish spots on its surface. The tumor was analyzed chemically, and the following values were obtained: cholesterol, 3 per cent, cholesterol ester, 2.6 per cent, lecithin, 2.9 per cent, fatty acids, 4 per cent, and total lipoids, 7 per cent. The wound healed by primary intention, and recent word from the patient is that he is steadily improving.

CASE 70—A woman aged 36 was admitted to the Mayo Clinic on Jan 4, 1937, complaining of pain and swelling of the right knee of several years' duration. The family history, past medical history and laboratory findings were all noncontributory. This patient had a long history of repeated trauma. In 1916 or 1917, while running

hard and attempting to jump a wire fence, her toe caught in the wire and she fell with all her weight on the right knee. This accident was followed by moderate soreness and stiffness in the knee for about a week, but she was able to get about. One year later the knee was struck a terrific blow by an ice hockey stick. This was followed by some stiffness, soreness and swelling for a few days.

The patient had no further trouble until August 1929. At this time she noticed a soft, painless lump about the size of a walnut on the lateral aspect of the knee, just below and lateral to the inferior pole of the patella. The mass was movable, and on flexion of the knee it became larger and "rode up" higher on the knee. Within about two weeks it increased to the size of a hen's egg and became hard. Light therapy was used, and a tight elastic bandage was worn for two weeks.

The patient was free of symptoms until March 1930. At this time, on stepping down from a curb, the knee was sharply twisted internally, the leg being



Fig 9 (case 70) —*A*, lateral roentgenogram of a knee containing a diffuse xanthoma of the synovial membrane, *B*, anteroposterior roentgenogram of the same knee

stationary. The patient experienced a slight twinge of pain and a "giving way" sensation but was able to walk with only a slight limp. She went to a physician at this time, and with a diagnosis of dislocated cartilage the knee was manipulated. During all this time the mass on the outer side of the knee was increasing in size.

In March 1931, while the patient was getting off a streetcar, the knee was again twisted, and she fell to the street. This accident caused severe pain and marked swelling, the knee reaching its maximal size (about twice normal) within one hour. The patient had at this time a burning sensation in the knee, which felt hot to the touch. Weight bearing produced excruciating pain, and the patient was required to remain in bed for several days. Pain and stiffness disappeared in about two weeks, but swelling never disappeared. About one month later a similar attack was brought about during dancing, and at this time a definite clicking sound was perceptible in the knee. Symptoms were again marked requiring rest

in bed for several days. The knee returned to normal (except for swelling) in about two weeks. The next year there were two more episodes of slipping, with the same symptoms. In 1932 after a treatment by a masseuse, she had an exacerbation of symptoms requiring rest in bed, this time for two weeks. After this she constantly wore an elastic knee cap, and for the next two years she had this "slipping out" of the knee on an average of about every two to three months. The mass on the lateral side of the joint reached its maximal size (that of a large hen's egg) in 1934 and by this time had attained the hardness of a rock. In August 1936 another attack was precipitated by wearing high-heeled shoes, and in November of the same year an attack occurred spontaneously. From that time on the patient had only slight twinges of pain in the knee and there were no more

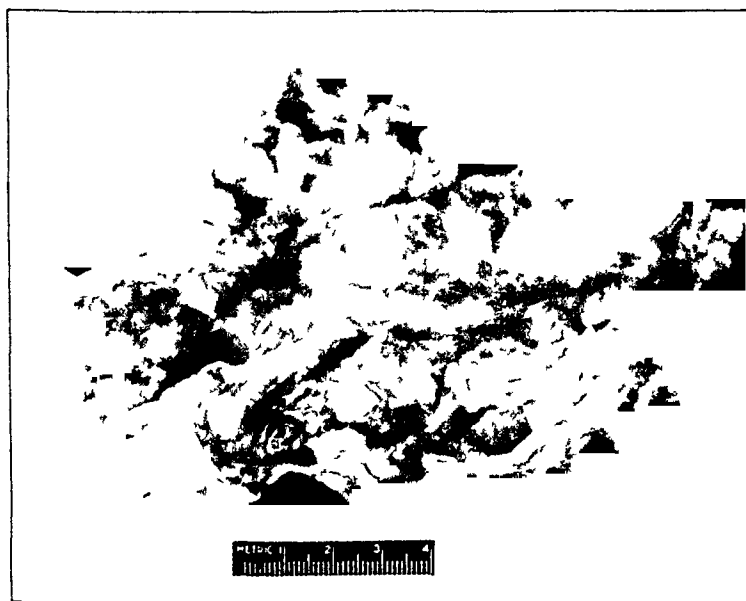


Fig 10 (case 70) —Gross appearance of synovial membrane removed for a diffuse xanthoma of this structure. Note the deeply pigmented villi.

slipping episodes. She always had full range of motion except during these attacks, and there never had been any locking.

On examination the right knee was 1.5 cm larger in diameter than the left (fig 9). There was marked crepitation in the joint on motion. A thickened, fibrous mass was palpable lateral to the patella. There were apparent thickening of the synovial membrane and evidence of fluid in the joint. The palpable mass slipped in and out of the joint on flexion and extension. There was no tenderness or local increase in temperature. On Feb 17, 1937, with the knee under a tourniquet, a short incision was made along the medial side of the patella and the patellar tendon. When the synovial membrane was opened, some brownish fluid escaped, some of which was sent for culture and was later reported sterile. A nodule the size of a large bean appeared in the wound immediately it was opened. The surrounding membrane was brownish, and there were long, stringy villi. The whole

membrane was thickened and had the same stinging villi. The cartilages on the surface of the joint were slightly but not completely eroded. The semilunar cartilages appeared to be in good condition. A complete synovectomy was performed (figs 10 and 11). A cast was applied from ankle to groin. Ten days later the cast was removed, and the patient began passive motion with the aid of an arthroplasty splint. On March 1 one roentgen treatment was given. Finally, on March 16, owing to poor progress in attaining motion, the knee was manipulated, with the patient under anesthesia. From then on motion gradually increased, and the patient was dismissed on March 23 with motion in the knee slowly improving. This patient was seen at the Mayo Clinic in May 1938, with no evidence of any recurrence. She said she had had trouble limbering up the knee, but at this time, there was full range of motion. There was no evidence of synovial thickening.

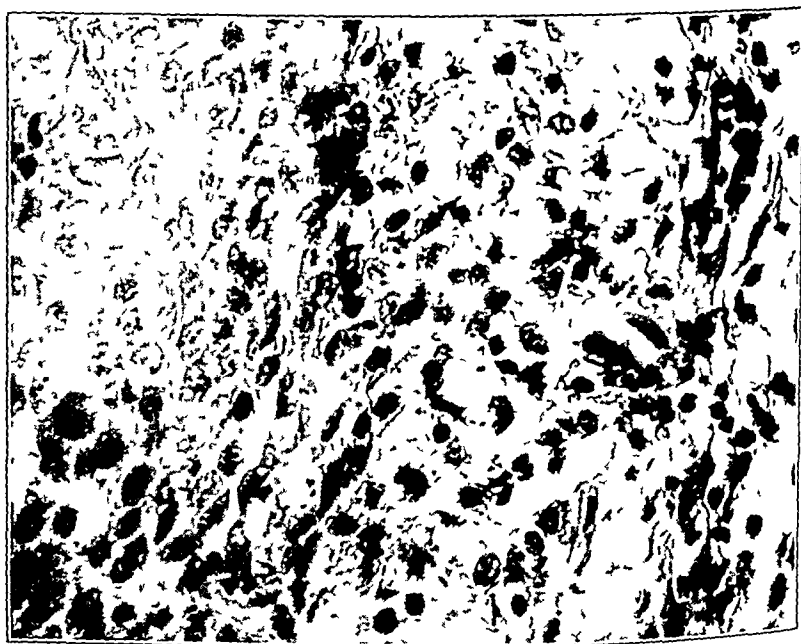


Fig 11 (case 70) —Xanthoma of the synovial membrane of the knee, showing large numbers of foam cells in the left half of the section and the typical endothelium-like cells of the stroma in the right half. $\times 400$

COMMENT

As has been brought out in the foregoing sections, xanthoma is a slowly growing, painless tumor, usually taking years to develop (five years and one month on the average in the cases reviewed in the literature and five and a half years in our own cases). It causes no disability except when it becomes large enough to interfere mechanically with adequate motion of the joints or proper function of the extremities. It varies in size and shape but in most cases is a firm round or oval lesion, averaging from 2.5 to 3 by 2 cm. It is slightly smaller when it occurs on the hands and finger than when it occurs on the feet.

and ankles. It occurs on the upper extremity two to three times as often as on the lower involving the finger most frequently. It is most common on the index and middle fingers as is shown by both series of cases. In the cases collected from the literature the flexor surface was involved 102 times and the extensor surface 41 times. In our group of cases the flexor surface was involved 28 times and the extensor surface 37 times. In the combined experiences the flexor surface was involved 130 times and the extensor surface 78 times. Although numerous writers have said that these tumors nearly always occur on the flexor surface they certainly must have based their conclusions on only a few cases as these figures show. It is conceivable that the tumors probably arise most often on the flexor surface, for this is the surface that is most frequently the site of trauma, however, we must conclude that both surfaces are affected and the surface on which the growth occurs cannot be used as a criterion for diagnosis.

Etiology—Age and Sex. The average age of the patients in the series collected from the literature was 37.5 years, as compared with an average of 44 years in our own group of patients. The greatest number fell in the third, fourth and fifth decades. In those patients seen at the Mayo Clinic the largest number fell in the fourth, fifth and sixth decades. In the cases reviewed here there were 71 per cent women and 29 per cent men, while in those in the literature there were only 55 per cent women and 46 per cent men. From these figures we can conclude that the two sexes are about evenly involved, the female predominating a little. We can also conclude that the average age is about 40 years, however, no age is immune, for tumors in a patient aged 82 have been reported by Malherbe,¹¹ and Garriett¹² spoke of a congenital tumor.

Heredity. The genetic factor plays a doubtful part, for we were able to find only 1 case in which it was present. The mother of the patient, treated here, had had a similar growth for forty years. Thannhauser and Magendantz¹³ reported the cases of 2 patients who were brother and sister. It appears, however, that this phase of the subject has been woefully neglected, and perhaps if the antecedents of these patients could have been thoroughly investigated, some factor linking the two together would have been discovered in many more cases. However, at present and from a statistical standpoint, this factor in the causation of this growth must be discarded.

Occupation. There is little help from the literature on this score for the occupation was listed too infrequently to be of value and when it was mentioned most of the writers disagreed on the part played by it. Of the patients observed here, over 50 per cent were housewives

and persons leading active lives, so perhaps occupation does play a larger part than most students of xanthoma are wont to believe

Trauma Many authors, such as Tourneau,¹³ Beekman,⁸ Broders,⁴⁸ Buxton,⁴² Janik,⁵⁰ Mason and Woolston,⁴⁹ King,⁹ Razemon and Bizard,⁹⁷ Young and Harris,⁹⁶ Grant and Stewart,⁵⁴ Kurtz,⁵⁴ and Garrett,⁴³ have stated the belief that trauma plays an important role in the production of these growths. The records in the literature are scanty. In less than half of the cases collected from it, a history of trauma was found in 10 per cent; thus, probably if there had been a record of the absence or presence of injury in all cases the figures would probably have reached about 40 per cent, for of the cases collected here such a history was obtained in 44 per cent. The more frequent occurrence of the tumors on the fingers and hands than on the forearm and arm and on the feet and ankles than on the rest of the extremity seems to substantiate this view. The probability is that the trauma responsible for the appearance of these growths is so mild, chronic or constant that the patient hesitates to provide the information, feeling it to be of little importance, and the examiner in most instances fails to elicit such data, for the same reason. In the same manner, infection in the extremity can be ascribed as a factor. We were able to find evidence of such infection in 23 per cent of our cases. Therefore, it is felt that trauma principally, and possibly infection, or both are the most important secondary factors in the production of these tumors, not severe, maiming trauma, but mild, unnoticeable constant injury concomitant with the daily routine of life. Zumtobel⁷⁰ and others have denied that infection or trauma plays a part in this condition, however, in the face of opposition we remain steadfast in our belief.

Lipoid Metabolism in the Production of Xanthoma Here again a great controversy arises as to the importance of alterations in lipoid metabolism in the causation of these tumors.⁹⁷ Let us first consider what is known about this subject up to the present time. There are three main groups of lipoids usually recognized in the blood that play a part in the metabolism of the body functions: first, lipoids in the strict sense, consisting of the nitrogenous phosphatides and cerebroside, the phosphatides being the so-called lecithins, cephalins and sphingomyelins. They are practically never found in the pure state but occur in connection with one another or with members of the rest of the group. They are found principally in the brain and adrenal cortex and are part of the fatty substances found in the organs of inter-

96 Young, F, and Harris, C. T. Complete Excision and Reconstruction of Both Achilles Tendons for Giant Cell Xanthoma, Surg, Gynec & Obst 61 662 669 (Nov.) 1935

97 Geschickter, C. F. Lipoid Tumors, Am J Cancer 21 617-641 (July) 1934

nal secretion. The second group includes cholesterol and its fatty acid esters, chiefly found in the adrenal cortex and the glands of internal secretion. The third group includes the glycerin esters, or neutral fats, which form the bulk of the fatty tissues of the body (Aschoff,⁹⁸ Thannhauser and Magendanz,⁷³ Games⁹⁹). Cholesterol, a hydrophilic colloid, was first isolated from gallstones by Comrad¹⁰⁰ in 1775. It is the chief member of the sterols with the formula $C_{27}H_{46}OH$, is an essential constituent of all living cells and is obtained chiefly from food but in part, according to Ingram,¹⁰¹ it may be synthesized in the body (Bodansky,¹⁰² Campbell,¹⁰³ Stewart¹⁰⁴). Its connection with xanthomatous changes was first pointed out by Pinkus and Pick¹⁰⁵ in 1908, and again in 1910 by Chauffard¹⁰⁶.

All these constituents are insoluble in water, thus they exist in the serum not in a dissolved form but in that of a finely dispersed stable emulsion. In order for these constituents to carry out their normal functions in the body their physical state must be maintained at all times. This stability of the emulsion is maintained by the proportions between the various lipoids and the albumin of the serum. If the concentration of any one element or of several elements is altered, the result, according to the laws of colloid chemistry, is a disturbance of the stable aqueous emulsion, the particles become coarser, the emulsion separates and finally, when conditions are suitable, there is a precipitation of one or all of the individual constituents and various lesions

98 Aschoff, L. Lectures on Pathology, New York, Paul B. Hoeber, 1924, pp. 1-33.

99 Games, M. T. Xanthomatosis, with Report of Case, *South M. J.* **26** 489-496 (June) 1933.

100 Cited by Bodansky¹⁰².

101 Ingram, J. T. Xanthomatosis Cutis and Hypercholesterolaemia. *Brit. J. Dermat.* **39** 335-346 (Aug-Sept) 1927.

102 Bodansky, M. Introduction to Physiological Chemistry, ed. 2, New York, J. Wiley & Sons, Inc., 1930, pp. 83-84.

103 Campbell, J. M. H. Critical Review. Cholesterol in Health and Disease, *Quart. J. Med.* **18** 393-422 (July) 1925.

104 Stewart, M. J. On the Cellular Reactions Induced by Local Deposits of Cholesterol in the Tissues, *J. Path. & Bact.* **19** 305-314, 1914-1915.

105 Cited by Rowland, R. S. Anomalies of Lipid Metabolism (Constitutional Pathologic Lipidoses), in Christian, H. A. Oxford Medicine, New York, Oxford University Press, 1931, vol. 4, pt. 1, pp. 214(3)-214(109), Xanthomatosis and the Reticulo-Endothelial System. Correlation of an Unidentified Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome), *Arch. Int. Med.* **42** 611-674 (Nov) 1928.

106 Chauffard, cited by McWhorter, J. E., and Weeks, C. Multiple Xanthoma of the Tendons, *Surg., Gynec. & Obst.* **40** 199-206 (Feb) 1925.

or diseases result, depending on the lipid that is precipitated (Bloch)¹⁰⁷ How the body maintains this constant level is not known, but Bloch,¹⁰⁸ Campbell,¹⁰³ McMeans¹⁰⁸ and many others concluded that the liver is the seat of control of this mechanism. McMeans concluded that the adrenals also play an important part.

The determination of any one constituent is not of much value, all must be determined quantitatively, and, above all, the ratio of the free and bound cholesterol must be known, for a disturbance in this ratio will alter the state of the stable emulsion and allow precipitation of one or more of the several blood lipids. Bloch,¹⁰⁷ Schaaf and Werner¹⁰⁹ and Tate¹¹⁰ stated that it is of more importance to know the relative values of the lipid content than to know the absolute values and that hypercholesteremia does not mean much if all the other elements are proportionally increased but that, if the ratio between the various constituents is altered, the factors necessary for the precipitation of the substances into the tissues are present. It will be noted that of our cases in which the values for blood lipids were determined, just such an alteration was observed in all but 2.

In the various diseases which result from disturbed lipid metabolism, the lipid that is deposited differs in each case. For example, in Gaucher's disease the cerebrosides are deposited, in Niemann-Pick's disease the phosphatides are deposited, and in Christian's syndrome and in the solitary and multiple xanthomas the lipids deposited are cholesterol and cholesterol esters (Gaines,⁹⁹ Rowland¹¹¹). In 50 per cent of our cases evidence of the presence of cholesterol deposits was observed. What, then, is the mechanism of production of hypercholesteremia? Chauffard¹⁰⁶ stated the belief that there are two types besides the increased cholesterol of alimentary origin: one is the result of disturbed hepatic function resulting in retention of cholesterol and is passive, the other is the result of endocrine secretion and is active. Others have concluded that the hypercholesteremia is entirely of alimentary origin. Schonheimer¹⁰⁹ came to the conclusion that the patient

107 Bloch, B. Metabolism, Endocrine Glands and Skin-Diseases with Special Reference to Acne Vulgaris and Xanthoma, *Brit J Dermat* **43** 61-87 (Feb) 1931

108 McMeans, J W. Tissue Reactions in Experimental Hypercholesterinemia, *J M Research* **33** 481-491 (Jan) 1916

109 Cited by Gruenfeld and Seelig ~

110 Tate, B C. Cutaneous Xanthomata Associated with Intermittent Diabetic Insipidus (High Blood-Fat and Normal Blood-Cholesterol), *Proc Roy Soc Med* **26** 1546, 1933

111 Rowland R S. Anomalies of Lipid Metabolism (Constitutional Pathologic Lipidoses), in Christian, H A. *Oxford Medicine*, New York: Oxford University Press, 1931, vol 4, pt 1, pp 214(3)-214(109)

may be able to absorb cholesterol but unable to excrete it and that this condition results in hypercholesteremia. Present day evidence, in spite of repeated experiments by many investigators, fails to place the cause of the increase or the alteration definitely in the ratio of the free and bound cholesterol. We are forced to conclude, however, that it does occur, and many writers have concluded that this is the primary factor in the production of these lesions, whether they are solitary or multiple. Among this group are Einaudi,¹¹ Ewing,¹¹ Pinkus and Pick,¹⁰⁷ Pingsheim,⁴¹ Weber,⁴⁵ Weil and Kirch,⁷ Arning,¹¹¹ Bonn,⁹⁷ Kusnetzowsky,¹¹¹ Schmidt and Levy,³ Dunn¹¹ and many others. Among authors who have opposed the hypothesis are Mason and Woolston,¹⁹ Stewart and Flint,³⁶ Young and Harris⁹⁶ and Ragins¹⁰

Although only a small group of personal cases are recorded in which the values for blood lipoids were studied, it is firmly believed that the alteration in lipid metabolism, whether it be an absolute one or one of changes in the ratio of the relative constituents (principally the cholesterol-cholesterol ester ratio), is the primary etiologic factor in the production of these tumors and that trauma or infection (or both) in the involved areas is a secondary factor which is present in every case.

Pathologic Picture—We have carefully recorded the pathologic picture of this tumor in a previous section of this paper, but we failed to explain the presence and origin of the various tissue elements. Let us, then, consider each separately.

The Foam Cell (*Schaumzelle*), or Xanthoma Cell. This cell was accurately described by Chambard¹¹⁶ and Torok¹¹⁶ over fifty years ago and at one time was suspected of being related to sebaceous gland cells and even of having a parasitic origin. Pinkus and Pick,¹⁰⁰ Aschoff⁹⁸ and Kawamura¹¹⁶ observed that these cells possess phagocytic properties and came to the conclusion that they are reticuloendothelial cells infiltrated with fatlike substances. Anitschkow¹¹⁶ definitely proved the identity of these cells with the histiocytes by showing their ability to pick up vital dyes, and Plewes¹¹⁷ has demonstrated the presence of thorotrast in the foam cells. We too have demonstrated

112 Ewing, J. Neoplastic Diseases. A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 274.

113 Cited by Weber⁴⁵

114 Kusnetzowsky, N. J. Ein Fall multipler xanthomatöser Granulome der Sehnen, Arch f klin Chir **124** 73-80, 1923, abstracted, Internat Abstr Surg **37** 587-588 (Dec.) 1923.

115 Cited by Stewart and Flint³⁶

116 Cited by Rowland¹¹¹

117 Plewes, L. W. Nature and Origin of the Xanthoma Cell. Arch Path **17** 177-186 (Feb.) 1934.

this characteristic by the presence of intracellular pigment in practically every tumor in which foam cells were present Weber,⁴⁰ Broders,⁷⁵ Melicow,¹¹⁸ Kolodny,¹¹⁹ Gonzalez-Agular⁵⁸ and many others have considered them phagocytic cells, members of that class of cells known as the reticuloendothelial system Pollitzer,¹²⁰ Mason and Woolston,⁴⁹ and Gailett⁴³ concluded that they are endothelial in origin Broders³ stated that they are lymphocytes that have taken on the special property of phagocytosis of fat particles

What is meant by the reticuloendothelial system? Under this heading are grouped various cellular elements because of their common properties of phagocytosis, reaction to vital dyes and a general similarity of function, they include (1) the reticular cells of the splenic pulp, lymphatic tissues and bone marrow, (2) the endothelial cells of the liver capillaries, lymph sinuses, bone marrow, splenic sinuses, suprarenal and hypophysial capillaries, and (3) the phagocytic cells in the connective tissue, of which there are tissue histiocytes, splenocytes and blood histiocytes (Aschoff,⁹⁸ Sacks,¹²¹ Rowland,¹²² Oppenheimer and Fishberg)¹²³

It is evident, then, that the origin of the foam cell from the reticuloendothelial system is established without any doubt

Now that we have established the identity of this cell, the next question that arises is how the cholesterol happens to appear there Aschoff⁹⁸ offered three possibilities (1) by infiltration, (2) by fatty decomposition, and (3) by fatty transformation He concluded, "that if fat transformation occurs," that is, transformation of the carbohydrates or protein reserve of cells into fat, "it must play only a very minor role and since fatty decomposition is either postmortem or necrobiotic, therefore pathological fat deposits can occur only in consequence of fatty infiltration which has its origin in the surrounding cell juices" Kawamura¹¹⁶ and Anitschkow,¹¹⁶ Rowland,¹²² Pinkus and Pick,¹⁰⁵

118 Melicow, M M Xanthic Lesions Report of Four Cases, Including Two of "Xanthomatosis" of the Kidney, J A M A **105** 768-774 (Sept 7) 1937

119 Kolodny, A Bone Sarcoma The Primary Malignant Tumors of Bone and the Giant Cell Tumor, Surg, Gynec & Obst (supp 1) **44** 1-214, 1927 Bone Sarcoma The Primary Malignant Tumors of Bone and the Giant Cell Tumor, Chicago, Surgical Publishing Company, 1927, p 186

120 Pollitzer, S The Nature of the Xanthomata, New York State J Med **70** 73-80 (July 15) 1899

121 Sacks, B The Reticulo-Endothelial System, Physiol Rev **6** 504-44 (July) 1926

122 Rowland, R S Xanthomatosis and the Reticulo-Endothelial System Correlation of an Undefined Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome) Arch Int Med **42** 611-674 (Nov) 1928 Footnote 111

123 Oppenheimer, B S, and Fishberg, A M Lipemia and Reticulo-Endothelial Apparatus, Arch Int Med **36** 667-681 (Nov) 1925

Levy, Osterlin,¹²⁴ and Smith¹²⁵ have expressed agreement with this hypothesis. Dewey,¹²⁶ Mason and Woolston,¹²⁷ and Archow¹²⁸ concluded that this is brought about by a fatty tissue degeneration. Karsening and Ortolan¹²⁹ expressed the opinion that the doubly refractile bodies originate within the foam cells. Weber,¹³⁰ Hummhusen and Migenandt¹³¹ and Weidman¹³² also concluded that these cells have the inherent property of being able to elaborate their fatty substance within the cellular body, that is, as Weber,¹³⁰ expressed it "it is due to lipodrophic activity on the part of the cell themselves."

It appears that the general consensus favors the infiltration process, and in view of the marked phagocytic property of the foam cell, as has been pointed out before, we are inclined to agree with this idea.

The Giant Cell.—Next we must consider the giant cell observed in this tumor. Mallory,¹³³ Dyle,¹³⁴ Hartman,¹³⁵ Weber,¹³⁶ Bellamy,¹³⁷ Broders,¹³⁸ and Rigns¹³⁹ have concluded that this is a giant cell of the foreign body type, resultant from the fusion of endothelial cells. It has been called into question here as in and in ridding the tumor of such irritant substances as particles of fat and pigment, and it is in regions in which such particles are present that the majority of these cells are found in the tumor. The morphologic similarity of the giant cell of these tumors to the osteoclasts has been pointed out by some. We believe not only that it is similar to the osteoclast but that the two cells are identical structures, displaying a difference only in their affinity for different foreign materials (Mallory,¹³³ Broders¹³⁸). Fontana¹⁴⁰ was the first to call attention to these giant cells seen in the xanthoma.

King, Bellamy,¹³⁷ Garrett¹⁴¹ and Weidman¹³² concluded that too much attention has been paid in the past to the foam cells and the giant cells and too little to the type cell. They repeated that the foam cells and foreign body giant cells are not constant in the tumor and that

124 Osterlin, F. J. Xanthosarcoma. *Ann Surg* **91** 613-615 (April) 1930.

125 Smith, C. The Histology and Nature of So Called Foam Cell Tumors with a Report of Four Cases of Endothelioma Xanthomatousum, *Surg Gynec & Obst* **14** 551-557 (May) 1912.

126 Dewey, K. Experimental Hypercholesterolemia, *Arch Int Med* **17** 757-785 (June) 1916.

127 Weidman, F. D. Xanthosarcoma of Cheek Succeeding Xanthosarcoma of the Forearm. Multiple Tumors Versus Metastasis, *Arch Surg* **34** 792-827 (May) 1937.

128 Mallory, F. B. Giant Cell Sarcoma. *J M Research* **24** 463-467 (April) 1911.

129 Cited by Plewes¹¹⁷.

130 Weidman, F. D. Studies in Hypercholesterolemia. III. The Approach to the Pathogenesis of Xanthomas, *Arch Dermat & Syph* **15** 659-668 (June) 1927.

determination of the true nature of the tumor should depend on the type cell of the stroma. We agree that the type cell is the same in each instance and that the giant cells and foam cells are found in other lesions beside this one, but in each of our own cases one or the other was present and in most cases both were seen, so that we have come to the conclusion that they both are characteristic elements of this tumor and definitely belong there. In addition, we believe that if each tumor could be thoroughly sectioned and studied, all the previously noted characteristics would always be found.

Pigment. This appears as yellowish brown granules in sections stained by the hematoxylin and eosin method and imparts the Berlin blue reaction with the iron stains. Bellamy,²¹ Stewart and Flint,²⁶ Mason and Woolston,¹⁰ Smith,¹³¹ and Janik,⁵⁰ besides others, agreed that this pigment is the result of the breaking up of the red corpuscles of extravasated blood in the tissues. According to Smith,¹³¹ Mason and Woolston,¹⁰ and Beekman,⁸ this pigment produces the reddish brown color of the tumor. Miller,¹⁰ quoted Wells as saying "that the brilliant orange-yellow color of the tumor is due to the presence of either carotin or xanthophyll pigments or both, which are normally present in the blood serum and are readily taken up and combined with cholesterol fatty acid esters, which are in themselves colorless."

The Type Cell. The type cell, or stroma cell, as has been mentioned, is morphologically similar to the endothelial cells, and in this conclusion many authors recently have concurred. We also believe that this is true. The fat content, although it may be a mixed type, spoken of by some as mixed steatosis, is in most cases, according to our belief and that of many others, made up chiefly of cholesterol or its esters and is in most instances intracellularly arranged.

Pathogenesis.—Each constituent of this tumor has been considered. What part does each play, and how does the tumor happen to develop? We do not agree with Geschickter and Copeland¹³² and Wahlgren⁶⁹ in the conclusion that it develops and originates from the sesamoid bones. We found no histologic evidence for such an origin of any of the tumors in our series, and in going over the roentgenograms of the patients we were unable to find sesamoid bones at the site of the lesions except in a very few cases. The facts that a large number of these tumors arise on the extensor surfaces and other sites were sesamoid

131 Smith, D. T. Method for Making a Differential Diagnosis Between Xanthomatous and Melanin Tumors from Frozen Sections, Based on a Study of One Hundred and Thirty Xanthomatous Tumors and Two Hundred Melanin Tumors, *Arch Surg* 8:908-917 (May) 1924.

132 Geschickter, C. F., and Copeland, M. M. Tumors of the Giant Cell Group. Pathologic Entity, *Arch Surg* 21:145-156 (July) 1930. Footnote 55.

bones are conspicuous by their absence and that the tumors are all morphologically alike lead one to doubt the authenticity of this hypothesis

We are convinced that the primary factor in production of this tumor is a preexisting alteration in the lipid metabolism in which there is either a marked disturbance in the absolute values of the blood lipoids or, even more important, a disturbance in the ratios of the various constituents, chiefly that of cholesterol to cholesterol esters and that the secondary factor is trauma or infection at the site of the lesion. Lubarsch¹³³ expressed the opinion that lymphatic stasis aids at this point in its production, this we are unable to support. We believe that at the time trauma or infection enters the picture minute hemorrhages occur within the tissue, lipoids and pigment are deposited by way of the circulation and a secondary response of the tissue occurs in which certain endothelium-like cells, foam cells, foreign body giant cells and adult connective tissue make their appearance. These changes develop slowly or rapidly, depending on the severity of the hemorrhage and the subsequent release of lipoids and pigment. As the process progresses, vascularity increases, more hemorrhages occur and the vicious cycle is established.

It has been shown that a severe injury will make one of these tumors grow rapidly, though it has been heretofore rather quiescent. This feature undoubtedly is due to an added large hemorrhage, as has been described. As this process is usually slow, a well defined capsule of connective tissue surrounds the mass producing a more or less firm yellow to reddish brown tumor. In addition, we also are of the belief that in most instances this tissue response starts in the synovial lining of the tendon sheaths or in the synovial membranes of the joints. In some cases this feature is not recorded, either owing to an oversight on the part of the surgeon or because of failure to determine the site of the tumor accurately enough. In spite of this we believe that in most cases if a careful study and dissection are carried out such a connection will be demonstrable.

Type of Lesion—The question now arises. What is the true nature of this lesion? Is it a benign tumor, a malignant tumor or only an inflammatory tissue reaction to various irritants? What name should be given to it and how should it be classified? We could name about thirty writers who believe it to be benign but we shall refer the reader to the literature for this information. At any rate most authors agree that it is always under all circumstances a benign growth. Harbitz¹³⁴ concluded that it is comparatively benign but should be classified probably as a sarcoma, whereas Hartman¹³⁵ expressed the opinion that

¹³³ Cited by Weir, op. cit.

there is always a potentiality of malignancy Krogus¹³⁴ stated that xanthomatous lesions occurring on the fingers should be considered as benign, while those observed on the palm of the hand, foot or forearm sooner or later reveal a more malignant character We agree that some of the tumors seen about the ankle are suspicious owing to their infiltrating nature, but in none of the cases were we ever able to find any signs of either local or general metastasis after a long period of observation, and as a result we have concluded that these lesions too are not potentially malignant

Buxton,⁴² Jebens,⁶² Razemon and Bizaid,⁹² Spiess,³¹ von Albertini,¹³⁰ Ragins,¹⁰ Bellamy,²¹ Stewart and Flint,⁴¹ Gorog,⁵⁹ Zumtobel,⁷⁰ Negrie and Canton,⁸³ Lecne and Moulouguet,¹⁷ Pique, Biachetto-Brian and Fasciolo⁷² and Heurtaux,¹⁴ all believe that these growths are true tumors, Bonhomme,¹⁸ Sonntag,⁹⁰ Kusnetzowsky,¹¹⁴ Wegelin,⁷⁹ Foot,¹³⁶ Ewing,¹¹⁻ Bloodgood,²⁴ Seyler⁴⁰ and Bussebaum⁶⁸ subscribed to the theory of the inflammatory (granulation tissue) nature of these lesions Yamakawa and Kashiwabara¹³⁷ and Kurtz⁵⁴ concluded that they are inflammatory but that, in addition, there is a secondary disturbance of the lipoid metabolism Wustmann⁸³ concluded that they are associated only with a cholesterol diathesis and are formed as a means of removing the excess of cholesterol from the blood Montgomery¹³⁸ says that "they histologically represent fibrous stages of xanthoma with a foreign-body giant-cell reaction"

Sonntag's⁹⁰ argument for the inflammatory origin of this growth was that the stroma is typical granulation tissue, consisting of fibroblasts, lymphocytes, polymorphonuclear leukocytes, partly sclerotic scar tissue, blood pigment and crystals of cholesterol, surrounded by giant cells In our group of tumors blood pigment, cholesterol crystals, foreign body giant cells and evidence of inflammation were observed

While this tumor does not represent a simple inflammatory process, neither does it represent a true neoplasia comparable, for example, to

134 Krogus, A Xanthosarcomas in Tendon Sheaths, *Finska lak-sällsk handl* **64** 102-121, 1922, abstracted, *J A M A* **79** 173 (July 8) 1922 Zur Kenntniss der s g Xanthosarcome der Sehnenscheiden, *Acta chir Scandinav* **55** 363-383 1922-1923, Xanthosarcomas of Tendon Sheaths, abstracted, *J A M A* **80** 592 (Feb 24) 1923 Footnote 39

135 Cited by Kling and Sashin⁹⁴

136 Foot, N C Report on a Case of Unusual Giant Cell Lymphogranuloma *Am J Clin Path* **6** 278-285 (May) 1936

137 Yamakawa, S, and Kashiwabara, M Lipoidemia and Xanthoma, *Tohoku J Exper Med* **3** 317-332 (Dec) 1922, abstracted, *J A M A* **80** 1495 (May 19) 1923

138 Montgomery, H Xanthomatosis A Systemic Disease, *Proc Staff Meet.* Mayo Clin **12** 641-644 (Oct 13) 1937

lipoma, myoma, carcinoma or sarcoma. Regardless of whether it is considered to be inflammatory or neoplastic or both, it is an undoubted entity which differs in its behavior from simple inflammation and from neoplasia and probably develops in the presence of a coexisting disturbed cholesterol metabolism and secondary trauma or infection. We are of the opinion that these tumors should be classified under the heading of the primary essential xanthomatoses and that they should be called xanthomas of the tendon sheaths and synovial membranes. Most writers believe that these tumors are benign, they fail to report any metastasis, we failed to find evidence of metastasis, and we therefore feel that the tumors should be called benign xanthomas of the tendon sheaths and synovial membranes. Finally, we agree with the classification presented by Thannhauser and Magendantz⁷³

Diagnosis—Given a man or woman about 40 years of age with a firm, oval or round subcutaneous mass, about 2 to 3 by 2 cm located on or associated with a tendon sheath, preferably the flexor, of the fingers, a mass that has been painlessly and slowly increasing in size, given, moreover, that the patient presents a history usually of previous trauma and that chemical study of his blood reveals an absolute increase in its lipoids or an alteration of the ratio of cholesterol to cholesterol esters and there is, in all likelihood, a xanthoma of the tendon sheath. If the lesion occurs in a joint—usually in the knee—the signs and symptoms are those of an internal derangement of that joint. There is usually a history of previous trauma. There may or may not be locking, depending on the type of tumor, that is, whether it is pedunculated or diffuse. The knee may be hot and painful or, in some instances, may cause little if any disturbance. The roentgenograms are usually normal. Aspiration of the joint reveals bloody fluid, but it must be remembered that bloody fluid may also be obtained from sarcoma of the synovial membrane, from the joint of a hemophilic, from a joint involved by a hemangioma or from a joint in which there has been recent or old trauma. A determination of the bilirubin content of this fluid by the icterus index method with the patient's blood serum as a control is at times helpful¹³⁹. In addition, if the cholesterol content of the aspirated fluid is high, this is positive evidence of the presence of a xanthoma (Kling and Sashin⁹⁴).

Differential Diagnosis—This tumor must be differentiated from chondroma, which is harder, lipoma, which is softer, carcinoma, which usually affects the skin, osteoma, which is harder and connected with the bone, and ganglion, which is usually on the extensor surface, near a joint and softer. Tumors of the muscle must be thought of, and

¹³⁹ Kling, D. H. Bilirubin in Effusions of the Joints. Method of Estimation and Significance, Arch Surg 20 17-25 (Jan) 1930

tendovaginitis and tuberculous dactylitis are possibilities. If the lesion is in the joints, one must consider all those conditions producing an internal derangement of the joint, but here examination of the articular fluid is of great help. The final and true diagnosis, of course, must in most cases be based on biopsy and surgical removal.

Treatment—Since these tumors have been definitely proved to be benign, without evidence of metastasis, conservative surgical treatment is the method of choice. Usually only local excision is necessary, if a recurrence takes place, as it does if the tumor has not been completely excised, a second excision should be performed, but never should a limb be sacrificed for what appears at first glance to be a sarcoma. The actual value of roentgen therapy in the treatment of these tumors is still questionable, and in most cases little, if any, response has been observed, however, this method will probably continue to be used as an adjunct to surgical removal and in the future may prove to be of benefit in those cases in which complete removal of the tumor is not possible. For the patient with high values for blood lipid a diet low in cholesterol should be prescribed for three to four months. At the end of this period the blood chemistry should again be checked, the subsequent course being determined by these findings.

CONCLUSIONS

As a result of a study of the literature and of the records of 70 patients treated at the Mayo Clinic since 1919 we have been able to conclude that xanthoma of the tendon sheaths and synovial membranes is a benign lesion associated primarily with an alteration in the lipid metabolism secondarily set off by trauma, infection, or both. It is classified under the general heading of the primary essential xanthomatoses.

REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomaly—Weyrauch¹ stated that the anomalies of renal rotation, exclusive of ectopic and fusional deformities, may be divided into four main types (1) ventral, or nomotation (rarely excessive rotation), (2) ventromedial, or incomplete rotation, (3) lateral rotation (reverse or excessive rotation) and (4) dorsal (excessive or reverse) rotation

The change in the position of the hilus renalis which takes place during early embryonic life results from a differential regional growth within the metanephros rather than from actual rotation of the entire organ. Hypotheses concerning the causation of anomalous rotation were advanced by Weyrauch, who emphasized such intrarenal forces as the organizing activity of the ureteral tree as opposed to any extrarenal mechanical influence. He discussed the clinical aspects of the condition and summarized 19 cases.

Bernhard-Kreis² reported a case of malformation in the urinary tract in which the patient, a girl 4 months old, died after four months

¹ Weyrauch, H M, Jr. Anomalies of Renal Rotation, Surg, Gynec & Obst 69 183-199 (Aug) 1939

² Bernhard-Kreis, E. Zur Kenntnis der angeborenen Fehlbildungen der ableitenden Harnwege, Schweiz med Wchnschr 69 221-223 (March 11) 1939

of acute intestinal intoxication. Necropsy revealed bilateral duplication of the ureters. The two right ureters joined at the wall of the bladder. The right ureteral orifice into the bladder was so narrow that it was almost completely closed. One of the left ureteral orifices opened into a large ureterocele in such a way as to compress the other left ureter, which opened normally back of the ureterocele. Death was caused by infection of the urinary tract.

Torsion—Weyrauch³ stated that renal torsion constitutes an abnormal, acquired rotation of the kidney on its vertical, anteroposterior or horizontal axis and is classified as vertical, transverse or horizontal torsion, respectively. Combined torsion also is possible. Accurate clinical diagnosis of the type of torsion present may be reached by study of the pyelogram, supplemented by lateral views.

The factors which influence renal torsion are the length and the point of attachment of the vascular pedicle, the limitation of the mobility of the ureter in an upward direction, the firm, compact consistency of the kidney and the contour of the unyielding lumbar hollow.

Although it was found impossible to localize a mass to the peritoneum, retroperitoneum or kidney proper on the basis of the type of torsion produced, in general it may be said that a mass impinging upon the central portion of the kidney is more likely than not to produce vertical torsion, whereas one at either renal pole will cause the transverse or horizontal type.

Ventral displacement of the entire kidney or upper portion of the ureter is pathognomonic of a retroperitoneal tumor. Localized distortion of the renal pelvis other than mild compression is distinctive of an intrarenal mass. Enlargements of the liver and spleen may produce any type of renal torsion and result in a downward and medial displacement of the kidney.

Surgical Technique—Chauvin and Zananiri⁴ discussed the value of heminephrectomy in cases of supernumerary ureter in which abnormal outlets result in incontinence. Only 40 such cases in which heminephrectomy has been done have been published, these include 14 collected by Dossot (1926) and by Dewailly (1935), who added no new ones, and 25 collected by Eisendrath (1938), in which the operation was bilateral in 2 and was done for vaginal ectopy in 10 and for vulvar ectopy in 13. The single case of Pick and Hendrick brings the total to 40. In all these cases heminephrectomy was satisfactorily accomplished.

3 Weyrauch, H. M., Jr. The Significance of Renal Torsion in the Diagnosis of Retroperitoneal Tumors. Use of the Lateral Pyelogram, *J. Urol.* **41**: 877-892 (June) 1939.

4 Chauvin and Zananiri. Heminephrectomie pour abouchement vulvaire d'un uretere surnumeraire, *J. d'urolog.* **48**: 139-143 (Aug.) 1939.

It is surprising, however, to note the number of complete nephrectomies that are still done for this type of malformation.

Only two contraindications exist for heminephrectomy in such cases. One is the uselessness of conserving the normal kidney because it is too small, the other is the existence of a single pedicle opening into the kidney that is to be removed. Both are exceptional, and the second is not an absolute contraindication, since one pole in a solitary kidney may be safely resected.

Since kidneys of this type are always infected, vaccination of the patient before operation with a vaccine prepared from his septic urine is desirable. In the case reported, there had been constant incontinence from birth in a girl 18 years old in whom the power of voluntary micturition was nevertheless present, with normal functioning from four to six times a day. Cystoscopy on the right side revealed two orifices, of which one was blind 3 cm from the outlet and the other was normal. Urography demonstrated one normal pelvis on each side, thus suggesting probable bilateral double kidney, with the supernumerary half kidney on each side functioning too weakly to give an image. Only by meticulous examination of the vulva was there discovered, on the left side, behind the normal urinary meatus and about 1 cm distant from it, at the edge of the vaginal orifice, a minute ectopic ureteral meatus, which would permit the entrance of only a fine ureteral sound. The urine from this meatus contained pus and many colon bacilli. Retrograde urography, accomplished with difficulty through this minute meatus, disclosed megaloureter, with an enormous tube having a kink at its pelvic end. Its diameter was 4.5 cm in places, and it contained a few minute calices at its upper end. Roentgen examination of the lower part of the pelvis of the kidney on the same side showed that the ectopic ureter crossed the normal one several times, describing many sinuosities. This anomalous kidney, or half kidney, was situated above the sound kidney and about 2 cm away from it. After its removal recovery of the patient was uneventful for twenty-five days, at the end of which a fistula opened at the level of the incision, from which urine poured in abundance. The authors did not accept the explanation usually given in such cases, that a small amount of the pelvic wall had been left behind inadvertently, for they knew that this was not the case. They thought rather, that the fistula was caused by secondary necrosis, the site of which could not be determined. After three weeks the fistula closed and the patient experienced no further trouble.

Stone—Granoff⁵ presented a case in which a perinephric abscess on the left was accompanied by one secondary to pyonephrosis with

⁵ Granoff, M. A. Migration of Renal Stones Associated with Pyonephrosis and Perinephric Abscess into Lung, *J. Urol.* **42**: 302-310 (Sept.) 1939.

nephrolithiasis on the same side and in which the treatment had been surgical diainage twelve years prior to the death of the patient, followed by an intermittent discharge of pus and stones through the surgical incision for many years. Necropsy, following the death of the patient from cardiac failure, revealed an old, fibrous, contracted pyonephrotic left kidney enclosing renal stones, and a sinistral tract leading from the pelvis of this kidney to a cavity in the lower lobe of the left lung, which also contained renal stones physically and chemically identical with those found in the kidney. The stones had migrated from the kidney into the lung.

Although the thoracic complications of perinephric abscess and pyonephrosis are not common and occur principally in cases of long duration, their incidence is about as great as that of abdominal complications.

Invasion of the lung by a suppurative process requires preceding localized adhesive pleuritis, otherwise, empyema results.

Higgins⁶ says that prior to 1933 the incidence of postoperative recurrence of renal calculi at the Cleveland Clinic was 16.4 per cent. Since that year it has been reduced to 4.9 per cent by adding the high vitamin A, acid ash or alkaline ash diet to other postoperative measures, thereby controlling the pH of the urine.

The relation between infection and the formation of primary or recurrent calculi has been stressed for a long time. In Higgins' series of 200 cases of recurrent renal calculi, there was a coexisting renal infection in 81.5 per cent, whereas the urine was sterile in 18.5 per cent. Recurrent stones associated with infection were usually large and were composed of phosphates, carbonates or mixtures of these salts. Stones recurring in sterile urine usually were small and were composed of uric acid, cystine or oxalates.

Recurrence of calculi is more likely when an infection is present that is caused by organisms which possess the property of splitting urea, thus producing persistently alkaline urine and precipitating the alkaline salts, that is, phosphates and carbonates. In Higgins' series 9 per cent of the bacilli and 18 per cent of the staphylococci were of the urea-splitting type.

Focal infections were common, but there was no apparent relation between the organisms obtained by culture from these sites and those isolated from the urine.

Urograms taken intravenously showed evidence of urinary stasis in 72 per cent of the cases, although it was difficult to form an opinion as to whether stasis preceded or was subsequent to the formation of calculi.

⁶ Higgins, C. C. Factors in Recurrence of Renal Calculi, *J. A. M. A.* 113: 1460-1465 (Oct. 14) 1939.

Experimental and clinical observations have demonstrated the existence of a relation between deficiency of vitamin A in the diet and formation of renal calculi. The history alone does not provide sufficient evidence to enable one to state whether a patient is receiving or utilizing adequate amounts of vitamin A, and a biophotometric test should be a part of the examination of every patient who has calculous disease. Higgins and his associates prescribe vitamin A as a routine postoperative measure.

Hyperparathyroidism has been assigned an important role in renal lithiasis by various authors. However, in Higgins' series it was present in only about 0.1 per cent of the cases.

Metabolic factors may play an important part in the recurrence of stone. Cystinuria frequently is associated with calculi. Increasing the solubility of the cystine in the urine by the administration of alkalis diminishes the possibility of the formation or recurrence of stone. Likewise, attention to diet, metabolic factors and the maintenance of a pH of the urine unfavorable for the deposition of crystals are important in preventing the formation of stone and the recurrence of the other types of excretory calculus such as oxaluria, phosphaturia, xanthinuria and uraturia.

Surgical precautions for the reduction of recurrences consist of minimization of trauma in handling the kidney, performance of pelvic lithotomy instead of nephrolithotomy whenever possible, thorough lavage of the pelvis and calices, followed by use of a suction tube to remove clots, debris, fragments of stones or minute stones and sand, and adequate drainage of the kidney whenever nephrotomy is necessary or when a high degree of infection is present.

Tuberculosis—Herbst⁷ stated that the factors involved in the mortality and morbidity of renal tuberculosis are the recognition of *Mycobacterium tuberculosis* in the urine, the general resistance of the individual, the procedures instituted in treatment and the provision of adequate facilities and detailed direction of every individual affected.

The indications for search are (1) unilateral renal infection, (2) hematuria with no obvious explanation, (3) pyuria with no organisms demonstrable by ordinary staining methods, (4) persistent pyuria of any kind, (5) cystitis which does not respond to treatment after a reasonable period, (6) pyuria or dysuria in persons who have a history of tuberculosis or active extrarenary tuberculous lesions, with nodular lesions in the seminal tract, and (7) urographic evidence of the destruction of renal tissue.

⁷ Herbst, W. P. Renal Tuberculosis as a Community Problem, J. A. M. A. 113 371-373 (July 29) 1939.

The general resistance of the patient was cited as the most important single factor involved in the problem. Herbst pointed out that renal tuberculosis was found clinically by Thomas in approximately 4 per cent of the patients in Glen Lake Sanitarium. The economic status of a community influences the incidence. Climatic influences are vital. In certain climates there is practically no urinary tuberculosis even though pulmonary tuberculosis occurs. Food and vitamins are important in the general factor of resistance.

All things being equal, the sooner an advancing destructive lesion is recognized and removed the higher will be the percentage of cures and the lower will be the percentage of mortality and morbidity.

Medical societies should survey the situation and lead in accomplishing the following: standardization and provision of facilities for recognizing Myco tuberculosis in the urine, enlistment of the cooperation of civic agencies, lay organizations and local health departments in seeing that there are adequate facilities for hospitalizing and caring for patients and improvements in living conditions in general and standardization of laboratory methods and facilities for the identification of bacilli.

Community action on the part of any medical society in such endeavors as those mentioned previously would result in some degree in dispelling the prevailing public opinion that physicians are obstructive to the acquisition of cheap or free medical service and what is more important, would stamp physicians as authoritative, dynamic and sympathetic leaders in solving community health problems.

Keyes⁸ again advised closure of an incision in the loin without drainage after nephrectomy for tuberculosis.

He recited in brief the history of lumbar closure after nephrectomy for tuberculosis. In 1912, W. J. Mayo advised surgeons to close the wound in the loin after filling it with salt solution to displace the air without drainage unless the wound is soiled by rupture of the kidney or of its pelvis or unless a perinephritic abscess is present. He repeated this injunction in 1915, and Verne Hunt, in 1923, wrote as follows:

A sinus persisting after nephrectomy (for tuberculosis) is due to incomplete removal of the diseased tissue, persisting infection in the ureter, and the institution of drainage. The insertion of drainage tubes after nephrectomy for kidney tuberculosis is as inadvisable as for tuberculosis elsewhere.

A rigorous technic must be adhered to. Mayo's precaution of filling the wound with sterile solution to replace air and prevent scrotal emphysema such as has been reported by both Aschner and Keyes must be observed. It has been Keyes' custom to fill the loin with a 1:10,000 solution of acriflavine.

⁸ Keyes, E. L. Closure of Loin Wound Without Drainage After Nephrectomy for Tuberculosis, *J. Urol.* **42**: 496-499 (Oct.) 1939.

Keyes' first nephrectomy for tuberculosis was done in 1906. The patient had perineal and perinephric abscesses. A clamp was left on the pedicle. He died fourteen years later of tuberculosis. Clamps were left on the pedicles of the first 5 tuberculous kidneys which Keyes removed and on many others thereafter. He had no trouble after he learned that the clamp must not be unlocked before the fourth day or removed before the fifth. The loins in which clamps had been left healed badly. Seven sinuses lasted until the death of the patient, or at least two years, whereas only 1 healed in a month, 3 healed in six months and 5 healed in from seven to nine months.

Drained wounds gave better results. Four healed in a month, 1 in three months, 1 in six months, 1 in a year and 1 in thirty months, and 1 persisted until the death of the patient.

Keyes found that in his operations performed since 1912 by the Mayo technic, 29 wounds had primary union, and 20 were known to have reopened.

Forty-one of 49 sutured wounds healed in three months. Only 66 per cent of drained wounds healed as quickly as the sutured wounds.

Of the patients who survived the removal of tuberculous kidneys and were followed more than a year after operation, clamps had been left on the pedicle in 13. Four of these patients died of tuberculosis or of renal insufficiency. Of the 23 patients whose wounds were sutured without drainage and who were followed, 10 died of tuberculosis and 13 (more than half) remained alive and well.

After his experience, Keyes was profoundly impressed with the conclusion that in cases of renal tuberculosis the drain which is placed in the loin is responsible for mixed infection and for the sinus in the loin. If the sinus opens after complete closure, the opening need not imply a tempestuous or a prolonged convalescence. Today, drained operative wounds resulting from nephrectomy for renal tuberculosis heal well, undrained wounds heal better. Keyes stated the belief that the results of modern atraumatic surgical technic will be better than those he has obtained since the war, that is, closure of 21 of 23 incisions in the loin without any drain whatever and also of 2 sinuses, only 1 of which was a grave one. Surgeons are no longer timid about tying the renal artery, they should not be timid about closing the incision in the loin occasioned by nephrectomy for tuberculosis.

And by "complete closure" is meant no drain whatever.

Hydronephrosis—Priestley⁹ stated that many advances have been made during the past twenty years in the conservative surgical treatment of hydronephrosis, so that now many kidneys can be preserved which

⁹ Priestley, J. T. The Conservative Surgical Treatment of Non-Calculous Hydronephrosis, Surg, Gynec & Obst 68 832-841 (April) 1939

previously would have been considered irreparably damaged and would therefore have been removed. The exact type of operation indicated depends on the significant observations in each case.

If anomalous vessels are present and it is demonstrated that they are of importance in the production of hydronephrosis, one of several surgical procedures may be employed. The vessels may first be temporarily occluded to determine their importance in the blood supply of the lower pole of the kidney. If no undue change in color takes place during compression for several minutes, the vessels may be severed. Should the lower pole become very dark and a sharp line of demarcation appear between it and the main portion of the kidney, the vessels cannot be divided without producing an infarct in it. Under these circumstances, if the vessels are definitely obstructing the ureter, the ureteropelvic juncture may be severed and the ureter reimplanted into the pelvis on the opposite side of the vessels. If pyelectasis associated with anomalous vessels is extensive and the pelvic wall is thin and flabby, resection of the renal pelvis also may be performed.

High insertion of the ureter into the pelvis also may be a factor in the production and maintenance of hydronephrosis. This abnormality may be corrected by any of a variety of surgical procedures. In general, an operation which does not entirely sever the ureter from the pelvis is to be preferred, when feasible, because the blood and nerve supply to the upper portion of the ureter is not disturbed by it. One of the simplest and most satisfactory procedures consists of simple anastomosis between the ureter and pelvis, so-called ureteropyeloneostomy. In this operation a new opening is made between the most dependent portion of the pelvis and the ureter at the corresponding level. A second procedure, similar in principle to the Finney pyloroplasty, may be employed. The adjacent portions of the ureter and pelvis are incised in a straight line, and the cut edges are then united, the posterior edge of the pelvis to the posterior edge of the ureter and the anterior edge to the anterior edge. Another operation which Priestley has not seen described in the literature but which he has employed with satisfactory results is performed as follows. A longitudinal incision is made in the upper portion of the ureter which lies adjacent to the pelvis. This incision is carried down to a level which corresponds with the most dependent portion of the pelvis near (approximately 1 cm. from) the renal parenchyma of the lower pole. The dependent portion of the pelvis which lies between the lower pole of the kidney and the ureter is then resected, a wedge-shaped section being removed, with the base of the wedge directed downward and the apex reaching upward to the level of, or a little above, the ureteropelvic juncture. The anastomosis between the remaining portion of the pelvis and the longitudinal incision in the ureter is then completed in the

usual manner. The Y type of operation described by Foley also may be used in this type of case, although it was described by the author for the treatment of stricture of the ureteropelvic juncture.

Somewhat less conservative operations may at times appear advisable. Occasionally, it may seem necessary to sever the ureteropelvic juncture completely, to resect the upper portion of the ureter which lies adjacent to the pelvis and to reimplant the upper end of the ureter in the lowest portion of the pelvis. This procedure may or may not be combined with resection of the pelvis. If the pelvis is resected, the line of incision may be carried to within 1 cm. of the renal parenchyma, both on the anterior and on the posterior wall. The ureter is then inserted at the lower angle of the pelvis. This type of operation is best reserved for large hydronephroses in which the pelvis is thin and markedly dilated and has flattened and narrowed the upper portion of the ureter.

Many types of surgical procedure have been employed for the correction of hydronephrosis caused by narrowing of the lumen of the ureteropelvic juncture, with variable results. One of the simplest procedures technically employs the principle of the Heineke-Mikulicz pyloroplasty and is known as the "Fenger operation", however, ultimate results following this type of procedure have not been satisfactory. Schwyzer modified Fenger's operation by using a Y-shaped incision of which the diverging limbs are placed on the pelvis and the descending limb continues down the ureter. This incision is closed so that the dependent point of the triangular flap created on the pelvis is approximated to the lower end of the incision in the ureter. Foley modified this operation by placing the diverging limbs of the Y incision downward on the lower portion of the pelvis directly opposite the upper end of the ureter.

Occasionally, cases of abnormal renal ptosis associated with some degree of hydronephrosis and with pain, which appears to be of renal origin, are encountered. If the clinical diagnosis has been established and if definite stasis has been actually demonstrated, a pleasing result may follow immobilization of the kidney in such a position that undue angulation or kinking of the ureter or ureteropelvic juncture does not occur. Elaborate methods of fixation are unnecessary.

Hydronephrosis which results from various abnormalities in the lower portion of the urinary tract and from pathologic conditions entirely extrinsic to the urinary tract is not at all uncommon. In cases of this type, however, a local conservative operation on the kidney is seldom indicated. Occasionally, the surgeon encounters definite hydronephrosis without adequate anatomic explanation for its development.

At times, hydronephrosis may develop, usually in one segment of a duplicated kidney but occasionally in both. When hydronephrosis develops in one segment only and the other half of the kidney is functioning normally, a conservative operation rather than nephrectomy is desirable. In Priestley's experience, heminephrectomy is the operation which has given the most uniformly satisfactory results. The line of resection should be placed so that neither a calyx nor a pelvis is opened. If the involved segment is excised as a wedge-shaped section, the edges of the defect in the remaining portion of the kidney can be approximated. Occasionally, a unilateral fused kidney presents a definite hydronephrosis in one segment, with resultant symptoms. Generally, this may be treated in the same manner as hydronephrosis in one segment of a duplicated kidney. Hydronephrosis sometimes develops in an ectopic kidney. Nephrectomy gives the most uniformly satisfactory results in the treatment of kidneys of this type, provided that the other kidney is in good condition. Because of the abnormal position of the kidney and its unusual blood supply, conservative plastic operations are less often successful than in cases in which the kidney is normally placed. A horseshoe kidney which shows evidence of hydronephrosis usually presents a clearcut problem at the time it is exposed surgically. According to the causes of hydronephrosis, the surgical indications will vary. Ordinarily, plastic operations on the ureter and pelvis can be performed as easily on a horseshoe kidney as on a single kidney.

There are certain general surgical considerations that seem important in obtaining satisfactory results after plastic operations on the kidney. Absorbable suture material is universally employed. A single row of sutures is adequate. Drainage established by nephrostomy is widely recognized as a valuable adjunct to practically every plastic operation performed on the ureteropelvic juncture. With such provision for immediate drainage during the early postoperative period, the incidence of secondary nephrectomy and functional failure of operation is definitely reduced. The use of an indwelling catheter which traverses the lower part of the pole of the kidney, the lower calyx, the pelvis, the ureteropelvic juncture and the ureter in order, so-called ureteronephrostomy when any plastic procedure has been carried out at the ureteropelvic juncture, is of definite value. This catheter should remain in place for some time. Fixation of the kidney in a position which is most favorable to good drainage at the conclusion of a plastic operation is generally advisable. The wound always should be drained.

Stirling¹⁰ presented 3 cases of advanced pyelectasis, the first is of interest because of the size of the tumor, which contained more than

10 Stirling, W. C. Massive Hydronephrosis Complicated by Hydro-Ureter. Report of Three Cases, *J. Urol.* **42**: 520-533 (Oct.) 1939.

2 000 cc of fluid, and the question of diagnosis, the second was a rare case of subcapsular pseudohydronephrosis, and the third was one of advanced hydronephrosis and hydroureter resulting from carcinomatous infiltration of both ureteral walls

Marion¹¹ expressed the view that the urologist's attitude toward large hydronephroses, which in the past have been removed without discussion or scruple, should be more and more one of conservation. When a hydronephrosis of great size is met, it is absolutely necessary to explore the opposite kidney, which is often equally dilated, and to learn its condition. Such a hydronephrosis is to be treated (1) by suppression of the obstacle that caused it, which may be a polar vessel, a kink or a ureteral or pelvic stone, (2) by elevating the kidney as high as possible and (3) by prolonged drainage of the kidney, until the pelvis has returned to approximately its normal size or until it tends to no further diminution of size. Capitonage of the renal pelvis and the placing of an indwelling ureteral catheter may be useful aids to reposition of the kidneys and to nephrostomy.

Nephrectomy is permissible only when the hydronephrosis is such as to make it impossible to bring the pyeloureteral region to view and to remove whatever is serving as an obstacle. Even then it should be resorted to only if the other kidney is sufficient in function. If this is not the case, such enormous hydronephroses should be treated by nephrostomy.

Sometimes a great hydronephrotic sac forms quietly and without painful symptoms of any kind. When attention is finally drawn to it, pyelographic examination is the means by which both the fact and the degree of dilatation can be determined, the pyelograms always should be bilateral, for in more than two thirds of cases the condition exists on both sides.

The rule is to conserve the kidney as long as the function of the parenchyma can still be assured, while this lasts, nephrectomy is not the treatment of choice. Marion has often saved hydronephrotic kidneys which, because of their dilatation, seemed valueless. It is evident that under these conditions the renal pelvis and calices do not resume their normal appearance, but the renal parenchyma takes on a much better function than was present when there was retention, and there is no longer aggravation of the lesion after the obstacle has been removed.

Conservation of such kidneys will be brought about by overcoming of the obstacle, high fixation of the kidney and drainage established by nephrostomy. Pyelographic examination will show how long this drain-

¹¹ Marion, G. Traitement conservateur des grandes hydronephroses, *J. d'urolog.* 48 5-19 (July) 1939

age should continue, usually the period will be three weeks to one month. A second pyelogram should then be made for comparison and a third a few weeks later. If the kidney is still diminishing, drainage may be continued longer yet. Again, injection of opaque fluid by the drainage catheter will show whether the fluid passes easily into the ureter and also will provide an idea of the time when the drain may be removed. After its removal, closure of the fistula is usually rapid if permeability of the ureter at its pelvic end is completely reestablished.

Results are to be regarded from two points of view, anatomic and functional. From the anatomic standpoint, it is certain that the normal size and relations never will be regained after large hydronephroses. But functionally the results of conservative treatment are almost always excellent, patients are relieved of their former suffering, and renal function, if it is not wholly normal, is at any rate notably improved. If results are not in the end all that has been hoped for, it is still possible to do nephrostomy or nephrectomy, according to conditions.

Tumor—Barney and Churchill¹² reported a case of adenocarcinoma of the kidney (hypernephroma). The patient was a woman of 52 in whom roentgenologic evidence of a metastatic nodule in the lung was the first sign of disease. Nephrectomy was performed five months later and fifteen months after nephrectomy the metastatic growth in the lung was excised by subtotal lobectomy. The patient was alive five years later, in good health and without evidence of disease.

Barney and Churchill emphasized two points in their case. The metastatic tumor in the lung from the adenocarcinoma of the kidney was not radiosensitive. If a metastatic growth apparently is solitary and accessible to surgical removal, it is definitely worth while to undertake its removal as well as that of the primary growth.

Perinephritic Abscess—Foulds¹³ reviewed the records of 49 patients suffering from perinephric abscess. The group consisted of 27 cases of so-called primary metastatic abscess, of which the abscess was secondary to preexisting renal disease in 16 and related to disease in adjoining organs in 6.

Foulds pointed out that in many cases the diagnosis was made late. Various aids to diagnosis were used. The shadow of the psoas muscles on the affected side was obliterated in approximately 70 per cent of the patients, and in many of the remainder it was blurred or indistinct. Roentgen evidence of scoliosis with the concavity toward the side on which the abscess was situated was noted in slightly less than half of

12 Barney, J. D., and Churchill, E. J. Adenocarcinoma of the Kidney with Metastasis to the Lung, *J. Urol.* **42** 269-276 (Sept.) 1939.

13 Foulds, G. S. Diagnosis of Perinephric Abscess, *J. Urol.* **42** 1-4 (July) 1939.

the cases. Scoliosis is produced by spasm of the lumbar muscles, caused by the abscess. Foulds pointed out that physical examination will reveal this spasm before it can be shown to exist by radiologic procedures and described a new sign in the diagnosis of perinephric abscess. He instructed the patient to stand erect and then to bend over, first to the suspected side and then to the contralateral side. The spasm of the lumbar muscles on the side of the abscess could be abundantly demonstrated by the ease with which the patient bent to this side and his inability to bend to the opposite side. Bending toward the side in which the abscess is situated caused little or no pain, but any attempt to bend to the contralateral side caused severe pain. This sign was noted in 10 successive patients, and for 3 of these 10 it enabled the author to make distinctly earlier diagnoses than would have been possible by other means. The average duration of symptoms prior to the patient's entering the hospital in this series was three and four-tenths weeks. Another nine days elapsed between admission of the patient to the hospital and operation. Any procedure which will shorten this period should prove to be useful.

Ptosis—Squillario¹⁴ recognized three types of nephroptosis: (1) a movable kidney that is entirely silent, with neither subjective nor objective symptoms, (2) a movable kidney with more or less severe subjective symptoms but little disturbance of function or with slight pathologic aspects and (3) a movable kidney with both subjective symptoms and objective anatomic changes, which may be grave.

The treatment of the first group is medical, consisting in the use of a belt and the administration of urinary antiseptics. For the second group, nephropexy is indicated to relieve pain, digestive disturbances and eventual nervous symptoms. For the third group, with which the most common complications are hydronephrosis, pyonephrosis with attacks of renal strangulation and sometimes grave hematuria, caused by venous stasis, treatment must be first addressed to the complication and then completed by nephropexy. The conditions may call for resection of an overdilated renal pelvis, freeing of intestinal adhesions, fixation of a ptosed colon or removal of an appendix.

General points to be observed when nephropexy is to be done are: (1) freeing the kidney, (2) placing it in its new site and fixing it, (3) inspecting the renal pelvis and ureter, (4) liberating the ureter and placing it in a new direction, (5) making as little change as possible in the renal pelvis and (6) varying the technic according to the complications that may be present. In many cases, perinephritis and pericolitis

¹⁴ Squillario, G. Sulle ptosi renali. Terapia chirurgica della ptosi renali. Arch. ital. di urol. **16** 127-151 (March-April) 1939.

which have been caused by inflammation of the kidney and the colon may be the cause of the patient's pain. Kinks and compressions may be found, or the surgeon may come on abnormal veins.

In the presence of a movable kidney, the typical lumbar incision is made below the twelfth rib, with a view not only to facilitating the freeing of the kidney and permitting fixation, but also to creating a more ample bed for the kidney, in which it will not be compressed.

Nephropexy may be done by fixation, which may be accomplished by transfixing of the renal parenchyma or partial or total decortication of the kidney, or by construction of perirenal "hammocks," which support the organ and allow the adhesions to form.

Caporale in 1934 made experiments in fixing the kidney by the perirenal subcapsular placement of a catgut ribbon, passing loops of the ribbon through the incisions, both longitudinally and transversely, to rope the kidney up. Because, however, it was difficult to obtain the material of this catgut ribbon, he substituted the perirenal subcapsular placement of catgut threads, running a series of four threads vertically and four transversely through the substance of the capsule, until these completely surrounded and supported it, like a hammock. After tying, the two upper ends were fixed in the tenth intercostal space, and the transverse threads were attached in the lumbar space. The technic is improved by exerting different traction on the various threads, so as to place the kidney in the best possible position, as near as possible to the normal.

In experiments on dogs, Caporale found that after seventy days no signs of the sutures could be found on the capsule. After fifty days solid adhesions had formed between the kidney and the posterior wall, consisting of fibrous bundles lying transversely to the direction of the capsule. A lesion of the parenchyma was not found in any dog.

This method is now regularly used in the clinic of the University of Turin, with excellent operative results. Provided the diagnosis is accurate, the proper indications present, the technic correct and the post-operative care suitably carried out, nephropexy by Caporale's method justifies all the hopes that have been pinned to it.

Cyst—Thevenard¹⁵ drew attention to a case in which he made the clinical and histologic diagnosis of pseudocancerous cyst of the kidney. In a man 66 years of age, the first indication of the presence of such a cyst was an extensive, sudden, spontaneous hemorrhage from the urinary tract, unaccompanied by pain. Three weeks later, hematuria of the same character again occurred, lasting thirty-six hours. An enormous mass was palpated on the left side, with smooth, regular outline, having all the characteristics of a renal tumor.

¹⁵ Thevenard, P. Kyste solitaire du rein a forme pseudo-concreuse, J d'urolog 47 478-482 (June) 1939

At operation a polar vessel was found and ligated, a large, two-lobed cyst occupied the hilum, with two veins passing in front of it and the other elements of the pedicle behind. Section of these two veins made it possible to draw the kidney forward and give access to the principal pedicle, thus accomplishing nephrectomy without other difficulty. The cyst occupied the entire kidney, leaving only a thin layer of parenchyma, with a few cystic nodules on the surface of the organ. It was multilocular, with two principal cavities, and its content was serous. At the upper pole could be seen the source of the hemorrhages, a dark spot, intensely congested, in one of the pyramids.

The pyelographic image taken in vivo was perfectly superimposable on that of the operative specimen, but the former was more instructive, the lower calix of the cyst appearing as if stretched between two fixed points, one renal and the other ureteral, freeing of adhesions at operation caused the specimen thereafter to present only the appearance of common hydronephrosis.

Although resection is evidently the ideal treatment for such a cyst, the intrahilar position made this type of operation rather complicated for the elderly patient concerned, and nephrectomy seemed safer than heminephrectomy, especially since there was basis for fear that malignant degeneration might have already begun, in view of the evident long duration of the cyst. The fact of the occurrence of two profuse hemorrhages served to strengthen this view. Although histologic examination showed this cyst to be benign, some other similar instances of the condition have been malignant, and it seemed unwise to risk the development of carcinoma a few months later in the kidney that served as its host. In such cases it would appear that performance of nephrectomy is preferable, but lack of statistics on the subject makes a definite judgment impossible at the present time.

Carbuncle—Ingrish¹⁶ reported 11 cases of metastatic staphylococcal infection of the kidney, proved by operation.

The primary focus in each of the 11 cases was a cutaneous suppurative lesion of no certain situation. The organism isolated from the involved kidney was *Staphylococcus aureus*.

A rather frequent diagnostic physical sign is a stony-hard costo-vertebral rigidity on the affected side. This is caused by a tremendous perinephric reaction and marked thickening of the fatty capsule, which becomes leathery. Fulness over the renal angle is characteristically absent except in cases in which an associated perinephric abscess is present.

¹⁶ Ingrish, G. A. Carbuncle of the Kidney. Report of Ten Cases, *J. Urol.* 42: 326-340 (Sept.) 1939.

The urine in the majority of cases was characteristically normal except for a slight trace of albumin, which undoubtedly was the result of toxic nephritis.

Intravenous urography in conjunction with the careful interpretation of a flat roentgenogram, when localizing symptoms are present and a history of a recent cutaneous lesion has been evinced, usually will suffice to make a diagnosis. Cystoscopic examination is seldom indicated.

Lesions on the anterior surface of the kidney are associated with abdominal symptoms which at times lead to an erroneous diagnosis of intra-abdominal disease.

Inglis¹⁶ stated that considerable confusion and differences of opinion exist in the literature as to treatment. As conservative treatment with incision and drainage failed to effect a cure in 2 of the 11 cases, it is felt that the toxic patient, especially if more than one lesion on the kidney is present, should be subjected to nephrectomy rather than to some form of conservative surgical intervention.

The postoperative management of the patients is important, as they show evidence of myocardial damage caused by prolonged and severe sepsis and for that reason they should be kept at rest in bed until the pulse approaches normal.

Renocolic Fistula—Ratliff and Barnes¹⁷ reported 2 cases of renocolic fistula between the left kidney and the descending portion of the colon. In 1 the condition was long standing and was tuberculous. The patient withstood nephrectomy but died after subsequent surgical intervention for closure of a fecal fistula. The other patient was acutely ill. The fistula was demonstrable by both pyelography and retrograde ureteral injection of methylthionine chloride (methylene blue). Recovery with closure of the fistula followed prolonged conservative treatment with ureteral drainage and pelvic lavage.

These cases emphasize the value of conservative treatment. It is apparent that in the first case, in which sinuses were present, drainage by catheter probably would have been of no avail, particularly in view of the tuberculous background. Nephrectomy was conservative treatment in this case. In the second case drainage by catheter was conservative therapy. In the presence of minimal nontuberculous infection without the complications of sinuses or ureteral obstruction, conservative treatment is justified.

Hydrocele—Woodruff and Rupert¹⁸ reported a case of hydrocele of the kidney. The patient was a boy 7 years of age who had multiple contusions and abrasions on the left side of his body following an auto-

17 Ratliff, R. K., and Barnes, A. C. Acquired Renocolic Fistula. Report of Two Cases, *J. Urol.* **42** 311-316 (Sept.) 1939.

18 Woodruff, S. R., and Rupert, H. S. Hydrocele Remis. *J. Urol.* **41** 919-927 (June) 1939.

mobile accident. He had severe abdominal pain in the upper left quadrant. A diagnosis of hydronephrosis was made, and an operation was performed the following day. A large accumulation of fluid was found in a well developed sac adherent to the surrounding tissues, which entirely surrounded the kidney. The first procedure was merely to drain the sac, and at a later operation the kidney was removed.

Woodruff and Rupert stated that the treatment for this condition—hydrocele renis—is surgical. They stated the belief that in instances in which there is a massive collection of fluid a two stage operation is safer than other measures and should be employed.

Lipomatosis—Cella¹⁹ collected 70 cases of lipomatosis of the kidney from the literature, to which he added 3 of his own. Gathering all into the form of a table, he showed that in every case the kidney had been altered by toxoinfectious or calculous processes or had undergone sclerosis, prior to the infiltration of fatty deposits, which gradually replaced the parenchyma and led to complete destruction of the organ. Such changes always precede the infiltration or replacement by adipose tissue.

Renal lipomatosis is a rare disease, found especially between the fiftieth and sixtieth years of age, more frequently on the left side, exceptionally on both and slightly more frequently among females than among males. The fat is an extrarenal tissue, derived from hypertrophy of the pelvis, which, following the elements of the renal pedicle, in general the vessels, infiltrates the parenchyma of the kidney. It can be readily differentiated from perirenal lipomatosis and from lipoma of the fatty capsule or of the renal parenchyma.

There are no pathognomonic symptoms, and, accordingly, the diagnosis of renal lipomatosis is clinically only presumptive. In fact, every case on record constituted a surgical or an anatomic observation. Since patients having the condition do not have a diagnosis pre-operatively, treatment naturally is directed toward combating the diseases which are its forerunners, such as infection, calculosis and other pathologic processes. But when, during the course of operation on the kidney, the renal parenchyma is found to be the seat of lipomatosis, nephrectomy or, better, removal of the entire fibrolipomatous mass is the treatment of choice. The surgeon should bear in mind, however, that because of the development of perirenal fat, which sometimes encircles the lipomatous kidney, the topography of the tissues surrounding the kidney is modified, and he must be on guard against causing the complications and accidents (hemorrhages or rupture of sacs with purulent content) which may arise when a kidney in this condition is operated on.

¹⁹ Cella, C. Sulla lipomatosi renale, Arch. ital. di urol. **16** 87-126 (Jan-Feb) 1939.

The prognosis depends on the causative background of the condition, and since the infectious and calculous conditions persist, the course is generally slow and progressive. In advanced stages of the disease all function of the kidney is lost. If it is not removed, it will deliquesce and fill the entire cavity with purulent fluid and with calculi, representing remnants of the calices and the pelvis. Finally the infection extends to the bladder and thence to the other kidney, and the patient will die, as occurred in 1 of Cella's cases. Usually, however the mass can be discovered and removed before such an extreme condition arises.

The condition *sine qua non* for fatty infiltration of the kidney is primary atrophy of the renal parenchyma, which often occurs with chronic suppurative processes associated with calculous or inflammatory processes. Rickards regarded this infiltration as physiologic compensation, always secondary to degeneration of the parenchyma. The infiltration may be limited to small zones of medullary substance, in early stages, or may involve the entire organ, in more advanced ones.

Fatty replacement of the kidney is in the opinion of Hamm and de Veer²⁰ a frequent accompaniment of a variety of lesions leading to atrophy or destruction of renal tissue. They selected 6 cases to illustrate mild, moderate and advanced grades of this condition. In 5 cases stones and infection were present. According to their observations, extensive fatty replacement of the kidney is encountered only among obese patients. The process is one of hyperplasia of the adipose tissue normally present in the renal sinus, and this hyperplasia is not the cause of renal atrophy or destruction but is a secondary phenomenon, which of itself is of little significance. According to the views set forth by Hamm and de Veer, designations connoting a neoplastic, invasive or destructive process should be discarded for one that clearly indicates the secondary nature of the process, and the latter should be used only to amplify the description of the pathologic lesion to which it is secondary. Of the many descriptive terms suggested the most apt seems to be "fatty replacement," employed, for example, as in "pyelonephritis with renal atrophy and fatty replacement."

Atrophic Pyelonephritis—Lieberthal²¹ stated that pyelonephritic contracture of the kidney consists of shrinkage of the renal substance as a result of chronic suppuration.

Various transitions to hydronephrosis and pyonephrosis are frequently seen. The development of the condition under discussion in a pure form depends on the presence of low grade suppuration and

20 Hamm, F. C., and de Veer, J. A. Fatty Replacement Following Renal Atrophy or Destruction, *J. Urol.* **41** 850-866 (June) 1939.

21 Lieberthal, F. Pyelonephritic Contracture of the Kidney, *Surg., Gynec. & Obst.* **69** 159-171 (Aug.) 1939.

usually of low grade obstruction. It is, therefore, not uncommonly seen in cases of pelvic calculus. It is most frequently confused both clinically and pathologically with renal hypoplasia and is usually unilateral.

The most important diagnostic observation is that of a marked functional defect in the involved kidney. The pyelogram reveals a pelvis which is of normal size or slightly dilated. Pyelonephritic contracture occasionally is bilateral. The symptoms may then resemble those of chronic glomerulonephritis with contracture. Unilateral pyelonephritic contracture may cause hypertension, which may be relieved by nephrectomy.

Necrosis—Larson and Bennett²² presented 2 cases of symmetric cortical necrosis of the kidneys demonstrated at necropsy. These cases were of particular interest because the necrosis was associated not with pregnancy but with acute delirious mania and lobar pneumonia. The renal lesion in both instances was ischemic infarction, with relatively little hemorrhage within the renal cortex. Both grossly and microscopically, the necrosis resembled the white softenings so commonly seen in the brain and myocardium, in which no pathologic process in the wall of the vessel and no thrombosis can be demonstrated. The thrombus found in the renal vein in 1 case was considered to be of secondary origin. The finding of multiple petechial hemorrhages in the mucosal surfaces of the body and in the parenchyma of the brain in the first case suggest generalized functional vascular disturbance similar to that commonly observed in fatal instances of acute delirious mania.

The cortical necrosis observed in 1 instance was less marked than that in the second, which could be explained by the fact that the immediate cause of death was lobar pneumonia and not the renal lesion per se.

Infected Wounds—Mathe²³ reported a case of overwhelming infection of a renal incision following nephropexy and sympathectomy, the infection was caused by an anaerobic streptococcus as well as by *Staph aureus*. This infection resisted all forms of treatment, including compression, surgical drainage, lavage with commonly used antiseptic solutions and the local and general use of chemotherapy. The anaerobic nature of the infective organism was diagnosed by special culture. Prompt cure followed the institution of serotherapy, which consisted of establishing the patient's tissue reactivity to antigen therapy to be used later by supplying her with intramuscular injections of preformed

22 Larson, C. P., and Bennett, R. J. Symmetrical Cortical Necrosis of the Kidneys. Report of Two Cases, *West J Surg* 47:481-484 (Aug) 1939.

23 Mathe, C. P. Diagnosis and Treatment of Secondary Anaerobic Infections of Kidney Wounds, *J Urol* 42:488-495 (Oct) 1939.

immune bodies contained in blood secured from donors previously immunized by a long course of injections of undenatured antigen obtained from the offending organisms. Spectacular cure followed the intradermal, subcutaneous and local injection of undenatured bacterial antigens. Anaerobic infections of renal incisions present an immunologic as well as a surgical problem, and cure is best obtained by the cooperation of the surgeon with the bacteriologist.

Selye²⁴ stated that experiments on the mouse indicate that testosterone propionate administered during two to three weeks causes marked enlargement of the kidneys. Histologically, such kidneys are characterized by pronounced hypertrophy of the epithelium of the proximal and distal convoluted tubules and of the epithelium lining the parietal lamina of Bowman's capsules.

ADRENAL TUMOR

Tenenbaum²⁵ reported a case of cortical carcinoma with operative recovery of the patient, although sixteen months after operation many of the symptoms had returned, suggesting recurrence of the tumor.

He stated that the risk of mortality in adrenocortical carcinoma is known to be high, especially in cases in which the metabolic type of the adrenocortical syndrome is in evidence. The stormy postoperative course of his patient is an illustration of the severe reaction following removal of the tumor. Fortunately, malignant tumors of the cortex, probably as a result of their more rapid growth, seem to affect the opposite adrenal cortex much less than do the benign hyperplasias and, as a rule, cause little or no atrophy. In addition, administration of sodium chloride and extract of adrenal cortex either routinely (immediately before and after operation) or at the first indication, has been of great assistance in the prevention of acute adrenal shock and in reducing the surgical risk of adrenalectomy.

The significance of intravenous urography in the differential diagnosis of adrenal tumor has been stressed and characteristic changes in the upper calix have been described which seem to offer a new pyelographic sign in the diagnosis of some of the tumors.

URETER

Transplantation—Riba²⁶ stated that the performance of a ureterocolonic plastic operation in the presence of infection or in a potentially

²⁴ Selye, H. The Effect of Testosterone on the Kidney, *J. Urol.* **42**: 637-641 (Oct.) 1939.

²⁵ Tenenbaum, J. Carcinoma of the Adrenal Cortex, *J. Urol.* **42**: 277-287 (Sept.) 1939.

²⁶ Riba, L. W. Ureteral Transplantations. An Experimental Study, *J. Urol.* **42**: 27-34 (July) 1939.

infected field may lead to immediate serious sepsis or result in a late, poorly functioning anastomosis

Use of the intact ureter permits a uniform safe attachment to the mucosa of the bowel, by primary healing. The chances for the development of an ascending infection after the first stage of the operation are minimal.

The problem is to obtain a permanent functioning fistula following the second procedure. A lateral anastomosis is likely to be followed by stenosis. Excision of a piece of mucosa during the second stage, plus a more careful approximation of the ureteral mucosa to the mucosa of the bowel, has given the best results experimentally. An excessive portion of free ureter projecting into the lumen of the bowel may predispose to infection and constriction of the new ureteral orifice.

Immediate surgical survival gives no assurance that late complications and fatalities may not occur. Statistical data on final results and fatalities are incomplete.

New operative technics should first be thoroughly investigated experimentally. At least one year's postoperative observation seems necessary for evaluation of a new procedure.

Wade²⁷ discussed the conditions for which he has found it necessary to perform the operation of vesical exclusion or deviation of the urinary stream. They include exstrophy of the bladder, subsymphysial vesical exstrophy or epispadias in the female, vesicovaginal fistulas arising from obstetric or surgical injury or from the use of radium, carcinoma and chronic vesical tuberculosis.

The simplest and safest procedure is to transplant the ureters onto the loins. Despite the disadvantages of continuous urinary drainage onto the surface of the body, this operation is still justified in the presence of advanced malignant disease in which the situation is desperate.

The standard procedure, however, is to transplant the ureter into the colon and rectum, thereby establishing a cloaca. In certain animals in which a cloaca exists naturally, it is noted that, even though the channel is common, portions of it serve separate functions, one portion being the urodeum, in which the urine is collected, and one portion being the proctodeum in which the intestinal contents gather. In the human being whose ureters are transplanted to the pelvic portion of the colon, it is found that comparatively soon a urodeum and proctodeum develop as can be demonstrated by excretory urography.

Wade reported that he uses the Coffey-Mayo technic, by means of which bilateral simultaneous implantation is done in all cases made possible by the use of intravenous infusions of isotonic solution of

²⁷ Wade, H. The Expectancy of Life After Ureteral Transplantation, Edinburgh M. J. 46 61-82 (Feb.) 1939.

sodium sulfate. This procedure promotes immediate renal secretion and profuse diuresis and prevents anuria, which might otherwise result from the obstructive edema at the site of the anastomoses.

Wade considered important in postoperative management (1) the use of a rectal tube continuously to prevent the accumulation of urine in the rectum and to prevent the passage of flatus, (2) intravenous infusions of isotonic solution of sodium sulfate and (3) small doses of solution of posterior pituitary (0.25 cc.) every six hours for over-distention of the bowel.

Sufficient time has elapsed since the use of this operation to estimate its effect on the expectancy of life. For this purpose it is necessary to select patients having had this operation who were in sound general health and free from disease but who by developmental error or accident have suffered irreparable damage to the urinary bladder.

Patients who have exstrophy of the bladder are in this category. Wade reviewed the history of 4 patients who had this condition who were operated on, respectively, thirty, twenty-eight, twelve and eleven years ago. They were all well and leading healthy useful lives at the time of writing. Under these circumstances, the operation of ureteral transplantation is a relatively safe procedure and fully warranted as a method of treatment for such distressing disabilities. The high mortality which follows the procedure at times especially in the presence of carcinoma of the bladder, is the result of the primary disease and not of any inherent disadvantages of the transplantation itself.

This fact is illustrated by Wade's statistics, which include the end results in 60 cases. The ureters were transplanted to the loin in 5 instances (eleven and twelve years ago) to a fistula in 1 and to the bowel in 54 (two stages, 14, one stage, 30, with a single kidney, 10).

The results in the whole series were as follows:

	Cases	Recoveries	Deaths
Nonmalignant conditions	27	20	7 (25.9%)
Carcinoma	33	16	17 (51.5%)
Total	60	36	24

Since January 1936, the results have improved, as is shown by the following tabulation:

	Cases	Recoveries	Deaths
Nonmalignant conditions	11	10	1* (9%)
Carcinoma	14	8	6 (43%)
Total	25	18	7

* Cervical carcinoma treated by radium with the formation of fistulas from the vagina into the bladder and rectum.

The high ultimate mortality in cases of vesical carcinoma is brought out by the statistics in the table, which include those on patients who died many months or years after the operation from the natural progress of their primary disease.

Wade concluded that when the urinary bladder has been so seriously damaged as to be incapable of repair the creation of a cloaca by transplantation of the ureters into the pelvic colon is indicated. The risk to life is not undue, and the expectancy of life is good.

Obstruction—Campbell²⁸ discussed the important ureteral obstructions which occur among children, the majority of such obstructions are congenital. Persistent pyuria and pain in the loin are the two most common primary symptoms. Gastrointestinal disturbances will be noted in approximately a fourth of the cases of unilateral obstruction and in more than half of the cases of bilateral obstruction. In most instances a thorough urologic examination will readily determine the correct diagnosis. The indications for urologic examination have been stated. It is important to impress on pediatricians and other practitioners (1) that children endure these instrumental investigations far better and with

Analytic Results

	Cases	Post operative Mortality	Ultimate Mortality	Survival *
Vesical carcinoma	27	13	23	4
Vesicovaginal fistula (obstetric injury)	9	0	0	9
Vesicovaginal fistula (radium burn)	3	2	2	1
Persistent vesical systole (tuberculosis)	6	2	4	2
Congenital abnormality	6	2	2	4
Urethral carcinoma	4	2	3	1
Intractable cystitis	3	0	0	3
Urethral stricture	2	2	2	0
Urethral fistula	1	1	1	0

* To the time of writing

fewer reactions than do their elders, (2) that cystoscopic reactions occur less often among the young and (3) that fear of an untoward reaction alone never should be considered a contraindication to urologic investigation for a child. Treatment in such cases usually can be conservative, and the patient should be given the benefit of conservatism so far as is compatible with good surgical judgment. In many instances advanced disease of the upper portion of the urinary tract consequent to the obstruction or the complicating infection will require radical surgical attack and frequently loss of the kidney. Campbell stated also that proper surgical attention to the child preoperatively, in the operating room and postoperatively will be rewarded by satisfactory results and a surprisingly low mortality.

Rudnick and Cornell²⁹ reported 38 cases of ureteral pain in which stricture of the ureter was demonstrated in 34, and ureteritis in 31.

²⁸ Campbell, M. F. Ureteral Obstruction in Children, *I Urol* **41** 650-678 (May) 1939.

²⁹ Rudnick, D. F., and Cornell, E. L. Clinical Manifestations of Stricture of the Ureter in Women, *I Urol* **41** 679-686 (May) 1939.

Abdominal or lumbar pain or discomfort is the prominent symptom. The symptoms are frequently periodic and often associated with menstruation. Vesical symptoms are not prominent.

The diagnosis is easily made by vaginal palpation of the ureters which are always tender. In many instances the pain of which the patients complain can thus be reproduced by the physician.

The urologist must not be content with being able to pass a no. 5-F catheter to rule out a stricture. Number 7 or no. 8 bulb-tipped catheters are preferable. The average dilatation should be to the diameter of a no. 10-F catheter. In 75 per cent of the cases one dilation suffices.

Passage of the ureteral catheter reproduced accurately the "ureteral pain" of which the patient complained in all but 3 cases.

Ureterocele—Huth³⁰ reported a case of ureterocele in which the ureter extruded from the bladder. The patient was a woman aged 27. When she was a child, a mass had suddenly protruded from the urethra and had been replaced. Two years previously she had experienced severe pain on vomiting and had felt that something was forcing itself through the neck of the bladder. On examination she had found a small, red, painful mass at the urinary meatus.

Cystoscopic examination demonstrated low grade cystitis. A smooth, round mass about the size of a hen's egg was seen in the left half of the bladder. The termination of this contour below was at the site of the left ureteral opening, where a narrow pedicle communicated with the mass, which was identified as an enormously dilated ureter. The wall was soft and permitted indentations by the ureteral catheter. The apex of the mass was red and apparently inflamed, probably because of repeated exposure through the urethral opening. A contrast medium was injected intravenously, and in twenty minutes a urogram showed the right kidney to be normal in size, shape and position and to be concentrating the dye in a normal manner. There was no dilatation of either the pelvis or the ureter, the orifice of which was normal. The left kidney was much enlarged. The left ureter was considerably enlarged. The ureterocele was shown by a large, normal shadow in the cystogram. At the ureteropelvic juncture there seemed to be a kink or obstruction, but there was little pyelectasis.

With the patient under ether anesthesia, the right ureter was dilated with the Neil Moore fin bougie and cut with a short wave cutting current. Later, the left ureter was fulgurated, which destroyed a large portion of the superior circumference. In neither operation was any bleeding experienced and the patient had no shock. Recovery was uneventful.

30 Huth, P. E. A Large Ureterocele Which Extruded from Female Bladder on Voiding. *J. Urol.* 42: 534-537 (Oct.) 1939.

Later, cystoscopic examination showed a large ureteral orifice on the left side. A cystogram, made with sodium iodide, showed reflux up the left ureter, but the ureter was much smaller than it had been before operation, and the kidney had assumed its normal contour. The right kidney and ureter appeared normal, and the bladder was normal.

One year later, the patient did not complain of any symptoms. Indigo carmine injected intravenously was eliminated from the right kidney in eight and one-half minutes and from the left kidney in three and one-half minutes. The general health of the patient was excellent.

BLADDER

Beer¹¹ discussed the surgical treatment of infiltrating carcinoma of the bladder.

In cases in which the tumor and the involved wall of the bladder can be excised, this type of operative treatment, often involving reimplantation of the ureter, gives the best results. With some of the more extensive growths total cystectomy, if feasible, gives surprisingly good results judged by five year cures. With other more or less extensive growth radon seeds may have to be introduced, by means of cystotomy or through a cystoscope. This is always a hit or miss affair, because the surgeon cannot accurately delimit the extent of the infiltrative process by sight or by palpation from within the bladder. Despite these handicaps, a small percentage of patients so treated seem to be definitely cured. The end results, however, are far inferior to those obtained in cases in which the lesion is resectable.

Urologists who have had an extensive series of patients (in Beer's clinic almost 700 patients have been treated) gradually have come to a better understanding of the problem involved, and it is most encouraging to see that the last report of the Registry, in 1936, confirms Beer's conclusions that surgical excision and resection give the best end results.

In his own experience Beer has found that there are, on the one hand, benign papillomas and, on the other, two types of carcinoma (1 *a*) papillary carcinoma with atypical cells plus invasion of the stroma and occasional thrombi of the lymph vessels (1 *b*) papillary tumors with these characteristics plus an infiltration and invasion of the wall of the bladder to varying depths and (2) more or less solid more or less nodular, infiltrating carcinoma extending well into the wall of the bladder and occasionally extending widely in a horizontal direction.

In a recent review by Beer on total cystectomy it was found that the more radical the surgical treatment the higher the percentage of

¹¹ Beer, F. The Surgical Treatment of Infiltrating Carcinoma of the Bladder. *Surg. Gynec. & Obst.* 69: 113-114 (1st) 1939.

five year cures In a series of 24 malignant tumors of the bladder for which total cystectomy had been performed, 6 patients died after the operation Of the 11 patients operated on up to five years ago, 2 died, the deaths being classified as operative Among the other 9 patients, who survived the operation, those who survived for five years or more constituted 55 per cent of the whole group In 88 cases of carcinoma of the bladder, papillary and infiltrating, Beer had 15 operative deaths Sixty-five patients could be followed to test the value of the therapy, and 24 were cured for five years

In closing, Beer emphasized the importance of learning the technic of partial cystectomy, with or without ureteral reimplantation, as well as the technic of total cystectomy with implantation of the ureters in the skin or in the bowel, because all other methods of approaching this most difficult problem are hit or miss procedures

Darget and Lange³² reported the results of treatment of tumors of the bladder by implantation of radium needles, with a statistical study of 60 cases Thirty patients were still alive at the time of writing The immediate mortality was 33 per cent Four other patients died in the following two months Thirty-two patients lived more than five years Of these, Darget and Lange considered 14 completely cured

Colby³³ reported a group of malignant tumors of the bladder in which the patients were treated by supervoltage roentgen irradiation with a recently devised million volt generator Although the series is entirely inadequate as a basis on which to evaluate fairly this form of treatment, certain tumors appear to be profoundly affected, with considerable regression Those portions of the tumor which project into the cavity of the bladder seem to be affected considerably more than those which have extended through the wall of the bladder Other tumors are affected little, if any, and are considered "radioresistant" It is not considered that supervoltage irradiation, in its present state takes the place of operation in instances of circumscribed cancer which can be adequately removed The doses so far employed are probably considerably less than it is possible to use, but more experience is necessary to standardize the dosage and to determine the ultimate effect The local and general untoward reaction of the tumors is less than with lower voltages and the regression more evident

De Waard³⁴ reported 2 cases of tumor of the urachus

32 Darget, R, and Lange, J Resultats du traitement des cancers de la vessie par l'implantation d'aiguilles de radium a vessie ouverte en un temps (statistique integrale actuelle) *J d'uroi* **47** 273-286 (April) 1939

33 Colby, F H Super-Voltage Radiation in the Treatment of Bladder Tumors, *J Urol* **42** 538-553 (Oct) 1939

34 De Waard, T Two Rare Cases of Bladder Tumor (Urachus Tumor) *J Urol* **42** 554-558 (Oct) 1939

In 1 case the patient was a woman aged 54 who had been experiencing recurring vesical trouble. Cystoscopic examination revealed diffuse cystitis. In the median line, in the upper part of the bladder, a slight, clearly outlined swelling could be noticed, in the center of which a tuft of fibers, such as were floating in the urine, could be made out protruding into the cavity of the bladder. A ureteral sound could be introduced about 2 cm through these fibers into what was, apparently, an existing duct or cavity. The urine from both kidneys was completely normal. The bladder was filled and the peritoneum was opened by suprapubic incision. A tumor the size of a mandarin was found in the wall of the bladder. The peritoneum had grown firmly to this in the place in which the peritoneal fold usually is found. It was impossible to remove the peritoneal covering, so an incision was made around it, and the abdominal cavity was opened. The tumor was found attached to a thick string of omentum which stretched in the direction of the gallbladder. This string was cut through, and the tumor was extraperitonealized. It was removed from the wall of the bladder, and the bladder was closed. A good result was obtained.

In the second case the patient was a 37 year old man who complained only of occasional pain in the lower portion of the abdomen. Cystoscopic examination demonstrated a small growth resembling a papilloma in the upper part of the bladder, which bled occasionally for several months. At a second cystoscopic examination a granulating defect was found in the region of the papillary growth. Operation, similar to that in the previous case, revealed a similar-sized tumor, which also could not be separated from the peritoneum. The tumor was removed.

At cystoscopic examination both the tumors were found to be covered with mucosa. In the first case there was a duct about 2 cm in depth and in the second there was a small suggestion of a similar duct. The diagnosis in the second case was colloid carcinoma.

Ulcer—Kretschmer³⁵ reported 138 cases of elusive ulcer of the bladder. There seems to be a prevailing opinion among some urologists that patients having this condition are never cured and that they must bear their condition until death. Not all urologists, however, share this point of view. In a recent article Crenshaw stated "that the end-results are better than they are generally believed to be. He found that 72 per cent of his patients stated that they were improved or cured, 59 per cent that they were greatly improved or cured and 40 per cent that they were cured. Crenshaw stated also that resection should be done more frequently than it is at the present time in suitable instances.

³⁵ Kretschmer H. I. Elusive Ulcer of the Bladder. A Report of One Hundred and Thirty Eight Cases. *J Urol* 42: 385-395 (Sept.) 1939.

In Kretschmer's series of cases the youngest patient was 20, and the oldest was 81. One hundred and nineteen of the patients were women, and 19 were men.

Some of the most striking results have been obtained in so-called early instances of the disease. Therefore, Kretschmer stressed the importance of obtaining a careful history and of bearing in mind the possibility that a patient experiencing frequent and painful urination may have an elusive ulcer. Frequency of urination was present in every instance. Generally mild at the onset of the disease, it is often temporarily relieved, but the disease is progressive, and urinary frequency, as well as pain on urination increases.

There is no standard treatment for elusive ulcer. Wide resection of the ulcer-bearing region has been practically discarded because of the relatively large number of recurrences. Among Kretschmer's patients, the condition recurred in 40 per cent. In his experience high voltage roentgen therapy has not been of any value, whether used alone or in combination with fulguration. Presacral neurectomy was without beneficial result. In some instances the use of a 2 per cent solution of silver nitrate with fulguration was apparently of some value.

The treatment most frequently employed is fulguration through the cystoscope, this generally is looked on as simple and safe. Frequently it is combined with dilation of the bladder by water.

In Kretschmer's series of 138 cases 105 were available for study, with the following results: patients cured, 20.37 per cent, greatly improved, 36.11 per cent, improved, 13.88 per cent and unchanged, 29.63 per cent.

Ectrophy—Russell³⁶ described a case of complicated ectrophy of the bladder in which the condition differed from the usual complicated ectopia vesicae in that (1) an anterior wall of the bladder was present but no "roof," (2) there was only one bowel, opening at the ileocecal region, (3) there were two vermiform appendices, (4) there was almost complete absence of the large intestine, (5) there was no evidence of external genitalia, (6) sacral meningocele occulta was present and (7) marked cystic swelling of the caudal end of the neurenteric canal was present.

The baby was a well formed full term infant whose weight at birth was 6½ pounds (2,948 Gm.) and who lived eleven days. There were no abnormalities of the head, neck, thorax or extremities.

Russell gave a detailed description, both gross and histologic, of the abnormal structures present and concluded that the case supports the Wood-Jones mechanical theory of the origin of ectrophy of the

36 Russell, K. F. A Case of Complicated Ectrophy of the Bladder Presenting Many Unusual Features, *Brit. J. Urol.* **11**: 31-47 (March) 1939.

bladder This theory postulates that at some stage in embryonic development overdistention of the bladder occurred with subsequent bursting of the anterior wall

In its support Wood-Jones contended (1) that urine is secreted by the fetus in utero and when a child is born who has an imperforate urethra all stages of vesical distention can be seen, (2) that cases of ectopia vesicae have been recorded in which occlusion of the cleft urethra was present and (3) that overdistention of systems other than the urinary system is seen in the presence of hydrocephalus and syringomyelocele He postulated that distention of the bladder is to ectopia vesicae what hydrocephalus is to anencephalia, or syringomyelocele is to spina bifida

The mechanical theory also would account for the wide separation of the pubic bones and the lateral rotation of the ilium and ischium, which are characteristic of the condition

There are several constant observations in the presence of complicated exstrophy which cannot be explained by a given theory and which are difficult to understand, namely, the fact that all patients suffering from complicated exstrophy have two vermiform appendices, whereas those suffering from simple exstrophy possess only one, and that the ileocecal region is the site of the openings of the bowel on the cloaca and two openings are present, one for the small bowel and one for the large bowel

Postoperative Care—Many chronic and serious lesions of the urinary tract have their origin in the postoperative care of the bladder, especially following gynecologic operations The danger lies not so much in catheterization as in urinary stagnation, because simple catheterization at times other than in the postoperative period is relatively harmless

After vaginal and pelvic operations near the region of the bladder there is practically always residual urine When the patient has been catheterized and bacteria introduced, it becomes important to prevent stasis of residual urine on resumption of voiding Intermittent catheterization, to this end, until the residuum is negligible will reduce the incidence of infections of the urinary tract

The ideal procedure is one which will do away with catheterization entirely, if possible Most reports on methods of promoting voiding are concerned with inducing the bladder to empty itself after postoperative retention has occurred These methods include the use of solution of posterior pituitary and of the parasympathetic stimulants, such as carbaminoycholine hydrochloride and acetylbetamethylcholine hydrochloride and the injection of an irritant such as a 2 per cent solution of boroglycerin or several ounces of air into the full bladder The

administration of acetylbetamethylcholine hydrochloride by mouth in doses of 25 mg is at times beneficial and is not associated with serious constitutional effects. However, hypodermic administration is dangerous and is accompanied by alarming constitutional effects, such as profuse sweating, salivation, fainting, involuntary micturition and defecation and marked decrease in blood pressure, and in 1 reported instance resulted in death.

Woodruff and Te Linde³⁷ reported a method which is aimed at prevention of distention by inducing the patient to void early and thus to reduce the necessity for catheterization. They instil 1 ounce (29.57 cc) of a 0.5 per cent aqueous solution of the disodium salt of 2,7-dibromo-4-hydroxymercurifluorescein (mercurochrome) into the bladder at the conclusion of the operation and at the same time instil into the rectum 1 liter of a 2 per cent solution of sodium bicarbonate containing 60 cc of liquid petrolatum. Studies showed that although the latter procedure did not aid voluntary micturition, it provided a good intake of alkaline fluid during the early postoperative period and facilitated early defecation.

Among 500 patients who had undergone pelvic laparotomy, the instillation of mercurochrome into the bladder reduced the incidence of catheterization to 6.5 per cent as compared with 51 per cent in a control series of patients who did not receive such instillation. The patients for whom the instillation was used voided earlier and in greater amounts, thus more completely emptying the bladder, than the patients in the control series. Postoperative infection of the urinary tract did not occur among any of the 500 patients who had undergone laparotomy except 3, each of whom had presented a definite history of infection of the urinary tract preoperatively.

This procedure is of no value with extensive plastic operations on the vagina. In such instances an indwelling male catheter should be used for the first week, and then catheterization should be used until residual urine no longer exists.

Changes During Pregnancy—Muellner³⁸ discussed the physiologic changes in the bladder occurring during pregnancy and the puerperium. He stated that during this period the bladder undergoes progressive changes in tone and capacity.

Beginning with the third month of gestation there is a gradual increase of vesical capacity and decrease in vesical tone, reaching extreme levels in the last trimester. The tone improves before the

37 Woodruff, J. D., and Te Linde, R. W. The Postoperative Care of the Urinary Bladder, *J. A. M. A.* **113** 1451-1454 (Oct. 14) 1939.

38 Muellner, S. R. Physiological Bladder Changes During Pregnancy and the Puerperium, *J. Urol.* **41** 691-695 (May) 1939.

termination of pregnancy The bladder empties without residual urine during pregnancy Post partum, the bladder capacity is likely to be largest, and there is considerable decrease in tone as compared with that of the ninth month Residual urine is common, and its amount may be large during this period, and it should be drained by catheter if infected The bladder returns to normal during six to eight weeks

PROSTATE

Hypertrophy—Thompson³⁹ presented a case in which transurethral resection was performed in the presence of marked renal insufficiency The patient was a man aged 52 who had 650 cc of residual urine The results of a study of the chemical picture of the blood were as follows urea, 488 mg per hundred cubic centimeters, and creatinine, 15.2 mg On the twenty-third day after his admission to the hospital, the urea content of the patient's blood was 124 mg per hundred cubic centimeters, and transurethral resection was performed, 19 Gm of prostatic tissue being removed The patient was dismissed from the hospital on the fourteenth postoperative day, or thirty-six days after his admission There was no residual urine at the time of dismissal

Habern⁴⁰ stated that certain factors have a distinct relation to the outcome of operation for obstruction of the vesical neck, especially because of the age of patients who have prostatic hyperplasia Some of these factors are (1) the general condition of the patient, (2) renal function and cardiovascular reserve, (3) appropriate preoperative and postoperative management and (4) the time, type and extent of operation

The "surgical" diseases of the kidney frequently caused by urinary obstruction and infection are entirely different in causation, pathologic aspects, treatment and prognosis, from the so-called medical diseases of the kidney, generally classified as "glomerular nephritis"

In the improvement and management of renal function, certain factors are emphasized, such as (1) drainage, (2) amount and types of fluids administered and (3) "extrarenal" factors in renal function

Carcinoma—Hinman and Smith⁴¹ stated that radical surgical treatment is the only method which will cure carcinoma of the prostate A decade ago, radium was used vigorously in the treatment of 14 patients,

39 Thompson, G J Transurethral Resection in the Presence of Marked Renal Insufficiency Report of a Case, Proc Staff Meet, Mayo Clin **14** 401-404 (June 28) 1939

40 Habern, H C Obstruction in the Neck of the Bladder Criteria of Operability, J Urol **42** 581-601 (Oct) 1939

41 Hinman, F, and Smith, D Carcinoma of the Prostate California & West Med **51** 235-241 (Oct) 1939

and more recently, with the advent of high voltage roentgen rays, the latter form of radiation was tried hopefully. Aside from relief of pain for some patients and possibly a slight prolongation of life, the results were most discouraging.

Only 3 of the 24 patients reported on by Hinman and Smith who had transurethral resection to relieve obstruction were alive at the time of writing, none have been alive longer than two years. Three had been treated for prostatism by suprapubic prostatectomy. Twenty-one were dead at the time of writing, all of these had died within three years after operation and most of them within one year, all died of carcinoma.

It is difficult to estimate the value, if any, of conservative prostatectomy, such as the perineal enucleation of hyperplastic tissue which is causing obstruction, without making an attempt to remove any of the carcinoma associated with it. The operation is purely palliative, it is an effort to relieve urinary distress and, in this sense, is comparable to transurethral resection. Of 58 patients thus treated in the series reported by Hinman and Smith, carcinoma had not been suspected before operation in 9, although the lesion was too far advanced to permit radical removal. Thirty-three patients were treated by the implantation of radon seeds, each from 1 to 3 millicuries in capacity, at intervals of 1 cm throughout the carcinomatous region at the time of operation. One of these patients lived four years, 1 five years and 1 seven years, but all died of carcinomatosis. More recently 5 others received intensive high voltage roentgen therapy, but none survived two years. One other patient, who did not receive irradiation, survived six years but died of recurrence. With these 4 exceptions, no patient lived longer than two years, and 29 died within a year.

In treating 20 patients listed as having had partial radical prostatectomy, it was found impossible, on attempting radical operation, to remove all the carcinoma because it had extended beyond the vesicles, either too far up the vas or into the bladder. Nine died of carcinoma within two years. One lived five years, 6 had lived less than two years at the time of writing. None was cured, but generally the patients have been more comfortable than the run of patients in either of the two groups previously mentioned.

For 21 of the 156 patients reported on by Hinman and Smith radical prostatectomy was possible. It was felt that all local portions of carcinoma had been removed at operation. Before operation none showed any clinical evidence of metastases. The seminal vesicles of 11 patients were invaded, however. Three patients died shortly after operation, 1 of pulmonary embolism, 1 of paralytic ileus and 1 of pneumonia. Six died afterward, having carcinoma at the time of death. Seven died with

no evidence of carcinoma, 3 of senility, 1 eight years and 2 seven years afterward. Five were living at the time of writing with no clinical evidence of carcinoma. 1 for seven years, 1 for two years and 3 less than one year. All had good control and no urinary complaint. On a conservative basis, the aforementioned figures indicate the cure of half of those treated radically.

Patients who clinically display evidence of having carcinoma so far advanced as to be incurable but who have no enlargement or urinary obstruction associated therewith may be left untreated, or else irradiation may be used when they suffer pain from pressure or extension.

Patients who have median bars and incurable carcinoma may be relieved temporarily by resection, but if severe infection or calcification is present radical prostatoseminal vesiculectomy will give the greatest, most enduring relief, and life may be prolonged by embedding radium in the local regions of carcinoma which are left.

Patients who have hyperplasia and incurable carcinoma may be treated by conservative prostatectomy supplemented by the full use of irradiation.

Belt⁴² reported that after careful physical examination of 25 patients he decided that the growth could be completely circumscribed by the radical perineal operation. For 18 of these, a close inspection of the specimen revealed the presence of carcinoma and showed the growth to be confined within the specimen. Ten of these 18 patients were living and well at the time of writing, after periods varying from three months to nine years. In 7 of the group of 25 patients, the carcinoma had extended to the cut edge of the part removed and, therefore, probably beyond it. The patients received massive high voltage roentgen therapy. Five were living and well at the time of writing, after periods varying from one to three years. One died of metastases after five years and one of the same cause after four years.

Eighty-eight of Belt's patients suffering from prostatic carcinoma were afforded relief from the obstruction of the vesical neck through electrosurgical resection. Forty-eight had metastases when they were first encountered. Forty had no demonstrable metastases and received vigorous high voltage roentgen therapy in the hope that growth would be arrested. Of the groups submitted to resection, those having had resection and high voltage roentgen therapy and those untreated except by resection to relieve obstruction were about equal in respect to length of life from the date of the onset of symptoms, but the patients who received roentgen therapy were in less pain and looked healthier than the others at the time of writing.

⁴² Belt, E., in discussion on Hinman and Smith⁴¹

Bumpus⁴³ stated that carcinoma of the prostate gland cannot be accurately compared with other forms of malignant growth because of its late occurrence. That patients who have a malignant growth of the prostate have the shortest expectancy of life of any patients suffering from malignant disease is certain to influence therapy. It is one thing to tell a person in the early forties, who has an expectancy of life of several decades, that radical surgical treatment has the possibility of curing him although it is accompanied with great risk, but it is another matter to inform the patriarch of 75, who has an expectancy of less than a decade, that he should risk a major radical procedure involving a high risk of mortality for the remote possibility of a cure.

Such advice is still further weakened by the fact that carcinoma of the prostate gland, unlike other malignant diseases, not only occurs late in life but is one of the slowest growing of all types of malignant disease. Numerous instances are on record of patients suffering from carcinoma of the prostate gland, proved by biopsy, who have lived for more than five years with no other form of treatment than relief of urinary obstruction, and several instances are recorded of patients who have survived for more than a decade. It is the slow growth of carcinoma of the prostate gland which has led to such confusion concerning its treatment.

In most malignant diseases, the number of three year controls is given as a criterion of the success or failure of treatment. Carcinoma of the prostate gland, when untreated, has an average duration of more than three years. Bumpus once traced 171 patients from the time of the occurrence of their first symptoms to death, and found that the average duration of life for them was three and one-quarter years.

Robinson, Gutman and Gutman⁴⁴ recorded the serum phosphatase activity at p_H 4.9 and at p_H 8.6 of 19 patients who had prostatic carcinoma with skeletal metastases. The "acid" phosphatase activity of the serum was found to exceed 30 units per hundred cubic centimeters in 16 of the 19 patients. Thirteen patients who had prostatic carcinoma *without* roentgenographically demonstrable metastases to bone and 6 who had benign prostatic hypertrophy were found to have serum "acid" phosphatase values within normal limits. Of the control series of more than 250 patients, those who had advanced Paget's disease and high serum "alkaline" phosphatase values showed some increase in serum phosphatase activity at p_H 4.9, but all patients who had early and moderately advanced Paget's disease had normal serum "acid" phosphatase values.

43 Bumpus, H. C., Jr., in discussion on Hinman and Smith.⁴¹

44 Robinson, J. N., Gutman, E. B., and Gutman, A. B. Clinical Significance of Increased Serum "Acid" Phosphatase in Patients with Bone Metastases Secondary to Prostatic Carcinoma. *J. Urol.* 42: 602-618 (Oct.) 1939.

From their experience and from the reports in the literature (44 cases in all), Robinson, Gutman and Gutman felt justified in concluding that increased serum "acid" phosphatase activity is consistent and specific enough in occurrence to be helpful in the differential diagnosis of prostatic carcinoma with skeletal metastases. The determination of serum "acid" phosphatase activity appears to be a useful supplement to the clinical and roentgenographic study of patients who have prostatic carcinoma, particularly if surgical procedures are contemplated. As regards prognosis, the presence of increased serum "acid" phosphatase activity in patients who have prostatic carcinoma implies dissemination of the primary tumor and in this sense has an unfavorable significance, an upward trend in serum "acid" phosphatase values may signify further metastatic involvement.

URETHRA

Carcinoma—Wishard and Bodner⁴⁵ reported a case of squamous cell carcinoma of the anterior portion of the urethra cured by amputation of the penis and postoperative irradiation. Approximately 125 cases of primary carcinoma of the male urethra are on record. The deep portion of the urethra is a little more often the seat of the lesion than is the anterior portion.

Causative factors include old age, predisposition, chronic irritation, infection, inflammation, stricture, trauma and benign papillomas.

Symptoms are produced by narrowing of the urethral lumen, formation of tumor and secondary infection with development of abscesses and fistulas.

The histologic structure of urethral carcinoma usually is that of squamous cell carcinoma. Other types are discussed. Metastases occur through the lymphatic system to the regional lymph nodes.

The prognosis is usually poor but would be better if patients could be treated earlier.

Treatment consists of early diagnosis, surgical intervention and high voltage irradiation. More frequent urethroscopic examination and biopsy for patients supposed to have irretractable strictures and peri-urethral abscesses which fail to improve would render the outlook more hopeful than it is now and would increase the number of cases reported as well as detect instances of the disease earlier.

The female urethra and vesical trigon⁴⁶ frequently are the seat of inflammatory lesions which give rise to the symptom complex of

⁴⁵ Wishard, W. N., Jr. and Bodner, H. Primary Carcinoma of the Male Urethra, *J Urol* **42** 35-46 (July) 1939.

⁴⁶ MacKenzie, D. W. and Seng, M. I. Common Conditions of the Neck of the Female Bladder and Urethra, *Canad M A J* **40** 428-432 (May) 1939.

increased frequency of urination, urgency, tenesmus, dysuria, urethral pain and hematuria, as well as the so-called bladder trouble, one of the most common disorders of women

Inflammatory lesions give rise to changes in tissue recognized as (1) trigonitis, (2) trigonitis cystica, (3) trigonitis pseudomembranosa, (4) chronic inflammatory nonspecific urethritis, (5) urethritis cystica, (6) stricture of the urethra, (7) caruncle of the urethra, (8) relaxation of the urethral sphincter, causing incontinence and (9) urinary fistula

In order to correlate the clinical with the pathologic picture, the histopathologic aspects of the vesical outlet and the urethra in the female were studied in 50 specimens obtained at necropsy

In the child two types of vesical neck and urethra were found. The most frequent observation was smooth mucosa without any invagination or perimucosal structures. The second normal type was a urethra which had mucosal invaginations situated just distal to the vesical orifice. These invaginations are exaggerated by relaxation of the surrounding structures. In the anterior third of the urethra, periurethral tubular structures distinct from Skene's glands are seen. They are absent in the inner third. Glandular cells, distinct from normal transitional cells, surrounding a small lumen and manifesting a definite secretory appearance, are found within the epithelial lining of the vesical neck of the urethra, of the urethral crypts and invaginations and of Skene's ducts.

In the adult patient the most striking observation was the almost universal presence of submucosal infections indicated by infiltration of round cells and other evidences of inflammation. There was proliferation of surface epithelium with cell nests and cell bud, cysts and fibrosis.

The changes are the result of repeated trauma caused by sexual cohabitation and childbearing and infection caused by those organisms which are continuously present about the external genitalia of the adult.

Clinical evidences of these changes are intermittent attacks of increased frequency of urination associated in the more severe phases of the condition with terminal tenesmus, a sensation of incomplete emptying of the bladder and, at times, hematuria. Vague indefinite pains arise in the urethra, or general pelvic discomfort referred to the back or into the thighs is present.

On urethral calibration with a sound or bougie a boule, infiltrations or at times even true strictures or a general contraction are found. Bleeding may occur after gentle and careful instrumentation. On cystourethroscopic examination, granulation of the urethra and trigon pedunculated cysts or sessile polyps and at times the characteristic changes of pseudomembranous trigonitis are seen.

In the acute phase of these infections the treatment consists in (1) forced administration of fluids, (2) heat in the form of vaginal douches and sitz baths, (3) sedative rectal suppositories, (4) mild silver salts instilled into the bladder and (5) alkalis or urinary antiseptics given by mouth as indicated

In the chronic phase, if a granular change predominates, stimulating applications, such as silver nitrate, are indicated. If the lesions are cystic, they should be destroyed by cauterization or electrocoagulation, if they are fibrotic dilations are indicated

For all lesions the basis of treatment is dilations of high degree

TESTES

Hypertrophy—Zide⁴⁷ stated that a comparison of the size of a series of normal adult testes with the larger or remaining testis in a group of cases of unilateral atrophy or orchidectomy revealed essentially no difference in average measurements. The largest testis of the normal group approximately equaled in length and width the largest testis present in the abnormal group. There is no evidence on the basis of this study that the adult human testis undergoes any appreciable compensatory hypertrophy after atrophy or removal of its mate

Tumor—Higgins and Buchert⁴⁸ stated that malignant tumors of the testicle may be divided into the homologous and the heterologous type. The former is comprised mainly of the sarcomas and seminomas, the latter consisting of mixed tumors of adult and embryonal tissue

There was a history of previous trauma in 19.4 per cent of the cases reported by Higgins and Buchert

Bilateral testicular tumors are rare. Neoplastic disease seems to involve the right testicle more often than the left. There are no pathognomonic signs, painless swelling of the testis being the first symptom in the vast majority of cases

The test for gonadotropic substance is valuable in diagnosis, prognosis and treatment

Metastasis takes place by way of two routes, namely, lymphatic extension and dissemination through the blood stream. The majority of lesions metastasize first to the retroperitoneal lymph nodes. The lungs and supraclavicular glands also are frequent sites of metastases

Simple castration, castration followed by roentgen or radium therapy, radical operation, Coley's toxin and roentgen or radium therapy alone, are the usual types of treatment

47 Zide, H. A. Does Compensatory Hypertrophy of the Adult Human Testis Occur? *J Urol* **42** 65-67 (July) 1939

48 Higgins, C. C., and Buchert, W. I. Malignant Tumors of the Testicle. A Review of Eighty-Three Cases, *Am J Surg* **43** 675-687 (March) 1939

Results of treatment are discouraging. The best results are obtained in cases in which there is no clinical evidence of metastasis. In the series reported by Higgins and Buchert, a combination of castration and roentgen therapy seemed to give the longest survival rate.

VAS DEFERENS

Surgical Treatment—Freiberg and Lepsky⁴⁹ reported a case of restoration of the continuity of the vas deferens.

A man, aged 33, eight years after having had vasectomy desired attempted restoration of the channel of the vas. With the patient under gas anesthesia, an incision was made in the upper half of the right side of the scrotum. The vas was isolated, and a side to side anastomosis of its upper and lower portions was made. A strand of silkworm catgut was passed through the anastomosis to keep it open until healing took place. A roentgenogram, made immediately after the operation, disclosed that both the upper and the lower portion of the vas were patent and also showed the presence of the contrast medium in the right seminal vesicle. Numerous specimens of semen obtained later showed a normal number of spermatozoa.

Perves and Duvergey⁵⁰ stated that, although normally the orifices of the ejaculatory ducts are physiologically closed and impermeable to injections or to a reflux from the urethra, in the presence of some acute infections they open wide and make such a reflux possible, from the urethra into the seminal vesicles and vasa deferentia. This gaping or opening is characteristic of all glandular orifices when infected, first they become paralyzed, then destructive lesions occur, which seem to favor a more nearly perfect drainage of the gland. There is thus a parallelism between disturbances concerning vesicorenal reflux and urethrovesiculodeferential reflux.

Perves and Duvergey demonstrated this reflux by means of retrograde urography (radiopaque oil) in 4 patients who came under their notice. It has also been demonstrable during micturition. They spoke of "passive" reflux in the former case and of "active" in the latter. In 2 of their cases the radiopaque oil entered the ejaculatory ducts but not the bladder, possibly because of obstruction at the neck of the bladder. In the other 2 some of the radiopaque oil entered the bladder and some the ejaculatory ducts.

49 Freiberg, H. B., and Lepsky, H. O. Restoration of the Continuity of the Vas Deferens Eight Years After Bilateral Vasectomy, *J. Urol.* **41**: 934-940 (June) 1939.

50 Perves, J., and Duvergey, H. Du reflux urethro-vesiculo-deferentiel, *I. d'urolog.* **48**: 97-113 (Aug.) 1939.

Sixteen cases of passive reflux have been reported in the literature in addition to the 4 herein placed on record. In 3 the vesicles alone received the reflux, in 7 the vasa deferentia alone received it, and in 4 the entire vesiculodeferential system received it. Nine patients were observed in the course of genital tuberculosis, 6 following prostatectomy and 5 during the presence of urethritis and common prostatitis. Although primary tuberculosis of the genital tract does not show any pathognomonic image in urethrographic examination, Chevassu stated the belief that in the absence of other information the urologist should regard the reflux as of tuberculous origin.

Perves and Duvergey explained the reflux as follows. In acute or subacute infections, the muscles lying beneath the inflamed mucosa have been subject to temporary atony, which becomes definite if the infection persists. The orifices, which are muscular structures, are affected by this process. It is then possible to conceive of the existence of *transient* refluxes of a *dynamic* nature or *definitive* refluxes if the infection is old.

Two factors are necessary for the production of reflux: (1) contractions of the bladder which drive the fluid into the prostatic portion of the urethra and (2) a slight obstacle situated below the verumontanum, contraction or spasm of the membranous sphincter. Then the opaque fluid, subjected to two pressures in opposite directions, forces the orifices of the more or less atonic ducts. Italian urologists, in order to obtain this reflux, fill the bladder with opaque substance and then make the patient urinate while they compress the urethra. For this active reflux to be present, no gross lesions at the verumontanum are necessary, paralysis of the urethral muscle or slight sclerosis of the verumontanum is enough. There is no proof that antiperistaltic contractions cause these refluxes, to date there has been no experimental control of this possibility. The frequency with which obstacles (strictures) of the urethra figure in the cases is striking.

Clinically, reflux is most frequently discovered during urethrographic examination. But the existence of inflammatory attacks of orchiepididymitis may lead the urologist to look for it. There is no doubt that rectal examination in instances of reflux discloses more or less disease of the prostate gland or seminal vesicles. Urethroscopic examination, on the other hand, furnishes more exact information than does rectal examination. Some authors note irregularity and abnormal rigidity of the prostatic portion of the urethra, making it difficult to insert instruments. Changes in the verumontanum are constant, as is inflammation either of the verumontanum, the ducts or the prostate gland. The orifices of the ducts are often open, sometimes the examiner can see veritable caverns that have destroyed some or all of the region of the verumontanum.

This reflux is not in itself grave, it is a symptom, and its prognosis is in strict relation to its cause. In the presence of genitourinary tuber-

culosis, it indicates rather advanced destruction, in the presence of other infections, it may diminish or disappear during the course of treatment. After prostatectomy, it causes pain only occasionally.

The present study shows that if fluid can pass into the vasa deferentia by reflux, so also may infection pass along this route, into the testis and epididymis, an observation that has been confirmed by the results of vasotomy systematically done by Marion's advice before prostatectomy. Suppression of attacks of epididymitis, formerly so frequent, by simple ligature and section of the vasa deferentia, proves the propagation of urethral pathologic agents by way of the ejaculatory ducts. As a general rule, therefore, in the presence of attacks of orchid-epididymitis, the urologist should first treat the urinary infection, making a urethroscopic examination of the region of the verumontanum and a rectal examination to determine the condition of the prostate gland and the seminal vesicles.

URINARY INFECTION

Secretan⁵¹ discussed the sterilizing effects of increased oxidation. He stated that the city of Paris uses oxidation to sterilize its water supply, and recent experiments have shown that it is bactericidal, especially for *Bacillus coli*. Secretan tried endovesical ozone therapy in 5 instances. He used a two way catheter, so that the pressure in the bladder never increased to the point at which an embolism might occur. The immediate results were good, but a few days later as many colon bacilli were found in the urine as had been present before treatment. Secretan concluded that ozone therapy, which is disagreeable to the patient and difficult for the physician to administer, produces no more satisfactory results than the ordinary methods of treatment.

URINARY CALCULI

Kretschmer and Brown⁵² studied the records of 950 cases of peptic ulcer and of 1,260 cases of urinary calculi to determine whether the administration of large amounts of alkalis in the treatment of ulcer tends to cause urinary stones. Of 680 patients suffering from ulcer who had received intensive treatment for an average of four months, it was found that 21 (3.1 per cent) gave a history of urinary calculus before they started to receive treatment for ulcer. By contrast, stone developed sometime after the treatment was instituted in only 33 patients (4.9 per cent). In many instances stone did not form until ten to twenty years after the treatment had been discontinued.

51 Secretan, M. Essais d'ozonothérapie endo-vésicale dans les colibacillooses urinaires, *Schweiz med Wchnschr* 69 193-196 (March 4) 1939.

52 Kretschmer, H. L. and Brown R. C. Do Alkalis Used in the Treatment of Peptic Ulcer Cause Kidney Stones? *J. A. M. A.* 113 1471-1475 (Oct 14) 1939.

This variation, of 1.8 per cent, is "not a grave indictment of the use of alkalis," especially since the figure may be modified by the fact that some of the patients may have had silent renal calculi at the time treatment was begun, and by the consideration that in a cross section of 680 persons approaching middle or later life a normal incidence of renal calculus is certain to exist.

Likewise, it was found that only 1.2 per cent of 1,260 patients suffering from urinary calculi had had previous treatment for ulcers with alkalis. These figures do not support the theory that alkalis used in the treatment of peptic ulcer tend to cause renal and ureteral stones.

UROLOGIC HYPERTENSION

Maher and Wosika⁵³ reported cardiovascular and urologic studies on 101 patients who presented both hypertension and urologic defects, together with a discussion of their potential relation. The 101 patients comprising this study were all of the Caucasian race, 59 were males and 42 were females.

Twenty-eight patients of this group were dead at the time of writing, necropsy had been done on 11 of these. Thirty-seven patients were still under observation, and with the remaining 36 contact had been lost.

In the group with diseases of the prostate, secondary diagnoses included cystitis, urethral stricture, prostatic stones, hypernephroma, hydronephrosis, perinephritis, pyelonephritis and other results of infection. Patients of the pyelonephritic group also had many secondary complications, and often it was difficult to identify the major lesion as such, making this a heterogeneous group. Complications therein embraced urethral and ureteral strictures, cystitis, hydronephrosis, cystocele, fibroids, nephroptosis, hypernephroma and atrophy of one kidney.

Maher and Wosika stated that there can be no doubt that complete obstruction of the lower portion of the urinary tract, for example by an enlarged prostate gland, produces a decrease in urinary function and is accompanied by hypertension. In the present series prostatic disease accounted for 53 per cent of the male patients who were affected by hypertension. In cases of complete obstruction there is ample evidence that decompression by catheterization allows an improvement in renal function and a decrease in blood pressure. Most of the patients presented had an obstruction low in the urinary tract. In a consideration of the next largest group, of 27 patients, in this series, suffering from chronic pyelonephritis and complications, obvious obstruction was not

⁵³ Maher, C. C., and Wosika, P. H. Urologic Hypertension. A Study of One Hundred and One Cases. *J. Urol.* **41**: 893-899 (June) 1939.

always readily demonstrable. The dominant factor concerning these patients was that of recurrent infection of the urinary tract with the minor element of obstruction.

Barney and Suby⁵⁴ reported a case involving unilateral renal disease with arterial hypertension afflicting a 10 year old girl. The patient was thought to have had salpingitis several years previously. Cystoscopic examination demonstrated a normal bladder. Catheters passed without difficulty to both kidneys, no urine was obtained from the right kidney, which was found infected and atrophic. The blood pressure varied from 185 systolic and 130 diastolic to 200 systolic and 170 diastolic, expressed in millimeters of mercury. At operation the small kidney was found and removed. During the twenty-one months elapsing between operation and the time of writing, the blood pressure had been only a little more than 100.

CHYLURIA

Ray and Rao⁵⁵ studied chyluria involving 254 of 12,386 patients who had filarial infestation. The incidence of chyluria in the presence of filariasis was 2.05 per cent, with a ratio of males to females of 9 to 1. For 42 patients careful investigation and study, including, in some cases, cystoscopic examination and excretory urography, were done.

The pathologic changes are largely the result of obstruction of the lymphatic system from inflammatory reaction caused by the presence of adult parasites, the continuous passage of microfilariae and the circulation of their toxins. The obstruction in the thoracic duct or cisterna chyli may be caused by the adult parasite, but more frequently it is the result of inflammatory change secondary to the presence of the parasites.

After the obstruction occurs, there is an attempt to form an effective collateral circulation which results in enormous dilatation of the regional lymphatic trunks. This may appear many years after the death of the adult parasites. These dilated trunks may rupture into the urinary tract, the alimentary tract or the pleural, peritoneal, pericardial and vaginal sacs. When the rupture is into the urinary tract, the chyluria is of renal origin in about 25 per cent of the cases and of vesical origin in about 70 per cent. In the remaining cases chyluria is of mixed origin.

Cystoscopic examination during the flow of chyle shows the characteristic point of leakage from the lymphatic varicosities immediately

54 Barney, J. D., and Suby, H. I. Unilateral Renal Disease with Arterial Hypertension. Report of a Case Apparently Cured Following Nephrectomy, New England J. Med. **220** 744-746 (May 4) 1939.

55 Ray, P. N., and Rao, S. S. Chyluria of Filarial Origin, Brit. J. Urol. **11** 48-64 (March) 1939.

behind the interureteric ridge or, if the chyluria is of renal origin, the cloudy efflux or the emergent clot at one ureteric orifice

With the aid of excretory urography, usually but not in every case, communications between the renal calices and the dilated perirenal lymphatic vessels are clearly displayed by the presence of delicate fibrils radiating from the kidneys. In some cases, instead of showing radiating fibrils, the renal outline merges with that of the dilated saccular lymphatic vessels. In nearly half the cases of renal chyluria some obstruction to, or displacement of, the ureters is demonstrated. It is caused either by adhesions or by the pressure of enlarged lymphatic nodes or sacculated lymph channels. The scope of retrograde pyelography is limited, but use of it is indicated in instances of stenosis and deviation of the ureter.

The mode of onset of the condition is spontaneous, but in nearly half the cases there is a history of injury of some sort. In the female patient, in the majority of instances, the condition appears to date from parturition. It is extremely rare in children. Strangury and renal colic result from the retention of clots. The flow is rarely prolonged beyond two or three weeks and generally subsides in about a week. The period of remission may be as short as three or four weeks but is generally much longer. The patient presents other gross signs of filarial lesions. Inguinal lymphatic varix is commonly present in the male patient.

With regard to treatment, no prophylaxis is of any avail, but the simple treatment of complete rest in bed, elimination of fat in the diet, use of aperients and elevation of the foot of the bed may abort an attack if promptly carried out. For the medical treatment of chyluria, intravenous injections of trypsinamide, 2 to 3 Gm. in 10 cc. of distilled water, are found to be effective. Cystoscopy and fulguration usually are successful when the leakage is slight. If clots are present, irrigation of the bladder with a 1:2,000 solution of silver nitrate prior to these measures will be found useful. In severe instances it may be necessary to institute continuous drainage of the bladder for twenty-four hours by means of an indwelling catheter. Patients who have the intractable form of the disease show some displacement of the ureters, and, unfortunately, the condition is bilateral. In instances of neglect or secondary infection, because of the presence of massive or decomposing clots, suprapubic cystotomy may have to be performed. Unilateral nephrectomy fortunately is seldom required. Successful lymphaticovenous anastomosis would provide a satisfactory short circuit for the obstruction to the cisterna chyli or the thoracic duct, but attempts to perform it have failed.

HERMAPHRODISM

Smith, Mack and Murray⁵⁶ reported a case of true hermaphroditism, the twenty-third reported case of proved true hermaphroditism and the seventh of bilateral ovotestis.

At operation it was found that the left gonad consisted of a thin film of testis completely enclosing a core of ovarian tissue.

It would be supposed that if the combined ovotestis were brought from the inguinal canal down into the labioscrotum the testis would find the new situation more suitable than would the ovary and would function more prominently. In this case, however, the opposite occurred. The ovarian portion of the ovotestis began to function actively and actually tended to destroy the testis by its own expansion.

Therapy with testicular and thymus extracts was instituted in the reported case in an attempt to destroy the function of the ovary and stimulate that of the testis. Although certain changes were noted during the first weeks of therapy, the menstrual cycle was not arrested, and surgical extirpation of the ovarian tissue was found to be necessary.

Eight months after all gonadal tissue was thought to have been removed, the patient continued to have strong sexual desires for women and frequent penile erections. Whether this was caused by some remaining testicular tissue or by psychic stimulation alone will not be known until after further observation.

In view of the frequency of occurrence of psychoses and neuroses attributed to sexual repression and maladjustment in structurally normal persons, it seems nothing short of miraculous that this patient, subjected constantly since early childhood to unusually severe psychic and emotional trauma, should be eminently sane and stable. On examining the literature, however, it is seen that such an apparently remarkable observation is the rule rather than the exception in similar cases.

Of the 20 cases reviewed by Young it was noted that "the libido or emotions of the patient corresponded to the manner in which the individual had been reared in all cases but one, in which no note was made. In the case reported by Smith, Mack and Murray, on the other hand, the emotions, or libido, were those of a male, although the patient had been reared and had lived the major portion of life as a female."

UROGRAPHY

Wilhelm⁵⁷ discussed the technic of vasoseminal vesiculography by way of scrotal vasotomy. This method, in contrast to catheterization

56 Smith, P. G., Mack, J. R., and Murray, M.: A Case of True Hermaphroditism, *J. Urol.* **41**: 780-800 (May) 1939.

57 Wilhelm, S. F.: Vaso-Seminal Vesiculography—Clinical and Experimental Application, *J. Urol.* **41**: 751-757 (May) 1939.

of the ejaculatory duct, is easily performed. Satisfactory seminal vesiculograms were made in 121 cases without untoward effects.

The emptying of the seminiferous tract following transurethral prostatic resection has been studied in 25 cases. In 3 of these, serial seminal vesiculograms revealed complete retention caused by obstruction of the ejaculatory duct.

In cases of obstructive sterility, vasoseminal vesiculographic examination affords graphic evidence as to the patency of the seminiferous pathways and also may reveal unsuspected lesions in the seminal vesicles. Its routine use before any anastomotic operation is decided on is recommended.

The emptying of the seminiferous tract has been studied by means of serial vasoseminal vesiculograms. It has been found that the seminal vesicles and vasa deferentia normally empty themselves by a slow, more or less constant flow, in addition to, and independent of, ejaculation.

News and Comment

Symposiums to Appear in Later Issues—During the year symposiums will be published on the following subjects

"Preoperative and Postoperative Care of Patients," composed of articles by Dr Cobb Pilcher, on neurosurgery, Dr Waltman Walters, on the stomach, Dr John Alexander, on the chest, Dr I S Ravdin, on the biliary tract, Dr John R Paine, on the small and large intestinal tracts, Dr Barrett Brown, on plastic surgery, Dr Leland S McKittrick, on diabetes, Dr Charles B Huggins on the genitourinary tract, and Dr Claude S Beck, on the heart and pericardium

"Treatment of Compound Fractures," which will include papers by Drs H Winnett Orr, Otto J Hermann, William O'Neill Sherman and William Darrach

"Diseases of the Esophagus Requiring Operation"

It is also proposed to publish in June or July a special issue in honor of Dr Dean Lewis' sixty-fifth birthday

Southeastern Surgical Congress—The eleventh annual meeting of the Southeastern Surgical Congress will be held at the Tutwiler Hotel, Birmingham, Ala, March 11 to 13, 1940

Dr R L Sanders, Memphis, Tenn, is president of the congress, and Dr B T Beasley, 701 Hurt Building, Atlanta, Ga, is secretary-treasurer

American Association for Study of Goiter—The next annual meeting of the American Association for the Study of Goiter will be held in Rochester, Minn, April 15 to 17, 1940 The program will consist of papers dealing with goiter and other diseases of the thyroid gland, "dry" clinics conducted by guests of the Association, and operative clinics conducted by the staff of the Mayo Clinic

The Van Meter prize award of \$300 and two honorable mentions will be given for the best essays submitted concerning original work on problems related to the thyroid gland

Further information regarding the meeting and the awards may be procured from the corresponding secretary, Dr W Blair Mosser, 133 Biddle Street, Kane, Pa

TUMORS OF THE LATERAL THYROID COMPONENT

L CLARENCE COHN, M D

AND

GEORGE A STEWART, M D

BALTIMORE

According to Schiager, the first references to aberrant thyroids were by von Haller in 1779, Albers in 1839 and Giuber in 1845, the first accurate description was by Porta in 1849, and the first extirpation was by Stanley in 1850

Hinterstoisser in 1888 described 3 cases of lateral aberrant thyroid tissue, and von Eiselberg in 1901 collected 11 cases. In 1906 Schiager collected 15 cases from the literature of the preceding fifty years and added 2 of his own, and in 1908 McGlannan reported 3 cases. Wohl in 1917 added 4 cases. In 1923 Parcelier, Venot and Bonnin collected 23 cases from the literature and added 2 of their own. These authors noted that the disease becomes manifest most frequently between the ages of 20 and 40.

Billings and Paul in 1925 made a resume of 34 previously reported cases and added 1 of their own, bringing the total to 35. They noted that 70 per cent of the tumors were papillary. Leech, Smith and Chute in 1928 reported 4 "lateral aberrant thyroid tumors" in nearly 4,000 cases of disease of the thyroid, showing that the incidence in their series was 0.1 per cent. They noted the similarity between papillary adenoma of the thyroid and papillary adenoma of aberrant thyroid tissue. Cattell in 1931 reported 13 cases and confirmed the observation of Parcelier and his associates that the disease begins at an early age. The ratio of females to males was 10 to 3, corresponding with the ratio among the other cases of disease of the thyroid. He suggested the possibility of a single origin for papillary tumors of the thyroid and papillary tumors of lateral aberrant thyroid tissue. In 1931 Dunhill reported 4 cases.

Moritz and Bayless in 1932 collected 122 cases from the literature and added 6 of their own. They showed that the greatest incidence is in the third decade, that the ratio of males to females is 1 to 3 and

that 15 per cent of the tumors are bilateral. In 1939 Crile reported 13 cases (in 5 of which there were papillary tumors of the thyroid), and concluded that "papillary tumors arising in thyroid tissue and in lateral aberrant thyroid tissue are remarkably benign" and that "when a papillary tumor is present in the thyroid and multiple nodules of the same histological structure are present in the lateral cervical region, these nodules should not be interpreted as incurable metastases from a carcinoma, but should be considered as multiple benign tumors and should be removed."

Among other recent authors who have reported cases are Guazon, Lewisohn, Lawton, Lazarus and Rosenthal, Eberts, Probst and Agness, Hentz, d'Abreu, Gretman and Russum and Schmeisser. A total of 156 cases have been reported.

Theories of the histogenesis of tumors of thyroid tissue beyond the capsule of the thyroid gland and of certain tumors within the thyroid gland are expounded largely from conclusions reached in the researches of embryologists on the morphogenesis of the normal human thyroid gland, from deductions reached in the study of patients with myxedema following excision of aberrant thyroid tissue and from autopsy material presenting congenitally defective thyroid tissue, as in the case of the myxedematous idiot reported by MacCallum and Fabry in 1907 and cited by Weller in 1933.

EMBRYOLOGY

In 1885, His traced the development of the thyroid gland from the mesobranchial field, the median lobe from the middle portion of the epithelium of the floor of the pharynx and the lateral lobes from the sides of this floor. Born concluded that the middle lobe develops from the epithelium of the floor of the pharynx and the lateral lobes from the fourth gill cleft. Tourneux and Verdun in 1897, from a study of 8 human embryos and 5 fetuses, advanced the theory that the thyroid gland arises from the pharyngeal complex by one medial and two lateral bodies. According to these authors, the median primordium first appears at the 3 mm stage, becomes successively enlarged, lobulated, "bilobed" and detached from the pharynx and in the 16 mm embryo is located in its typical definitive position. The lateral thyroid primordia, arising from the anterior walls of the fourth endodermal pouch, undergo simultaneous detachment from the pharynx.

This theory was opposed by Groos in 1910 and by Kingsbury in 1915. The former concluded that, although the ultimobranchial bodies are embedded in the thyroid gland, they are derived from the fifth branchial cleft rather than the fourth, the latter reached the conclusion (with reservations) that the ultimobranchial bodies, after a period of growth, finally disappear without leaving a trace. The assumption of these embryologists of the existence of a single median primordium

for the thyroid gland was accepted by the majority of contemporary workers in the allied clinical fields

The theory of origin of the thyroid gland from three distinct primordia has more recently (1933) been confirmed and greatly elaborated by Weller, who after studying 24 human embryos and other material, although recognizing the morphologic changes in the "lateral

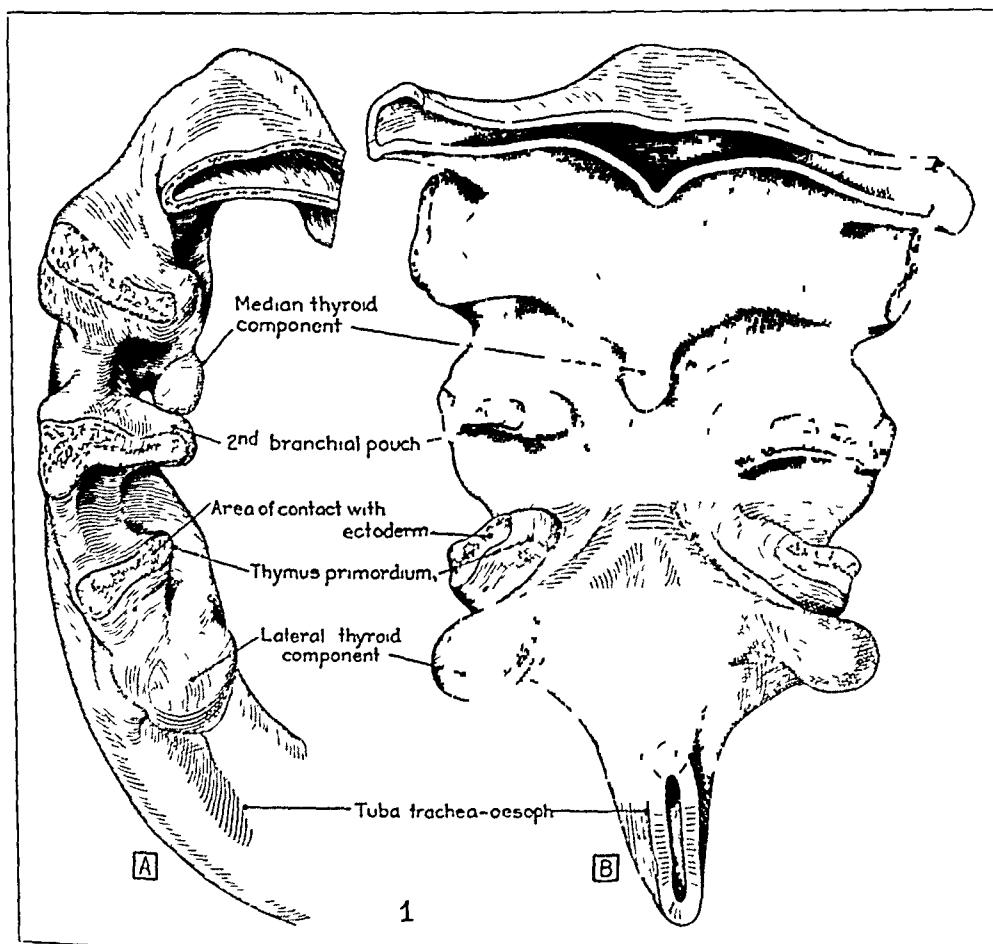


Fig 1—*A*, lateral aspect of the pharyngeal and primordial epithelium of a 4 mm embryo *B*, ventral aspect of the same (Copied from Weller, G L, Jr Development of the Thyroid, Parathyroid and Thymus Glands, Publication 443, Carnegie Institute of Washington, 1933)

thyroid component" described by Kingsbury, disagreed with his conclusions and estimated that the median and the two lateral primordia each contribute about one third of the tissue to the definitive thyroid gland and in the 13 mm embryo fuse into a morphologically single structure which histologically is composed of two distinct types of tissue (figs 1, 2 and 3)

Aberrant thyroid tissue deposited during migration of the median primordium has been reported as occurring in various locations in the midline of the neck, from the foramen cecum to the definitive thyroid gland. Thyroid tissue has also been reported as occurring in the nasopharynx, larynx, trachea, esophagus, mediastinum, pleura, pericardium, ovary and long bones. The present study is limited to the consideration of tumors of thyroid tissue located in the lateral regions of the neck, with and without tumors in the thyroid gland resembling them histologically.

CLASSIFICATION OF CASES

There have been collected in the Surgical Pathological Laboratory of the Johns Hopkins Hospital during the forty-five year period from 1893 to 1938 the records and sections of 20 cases in which tumors of lateral

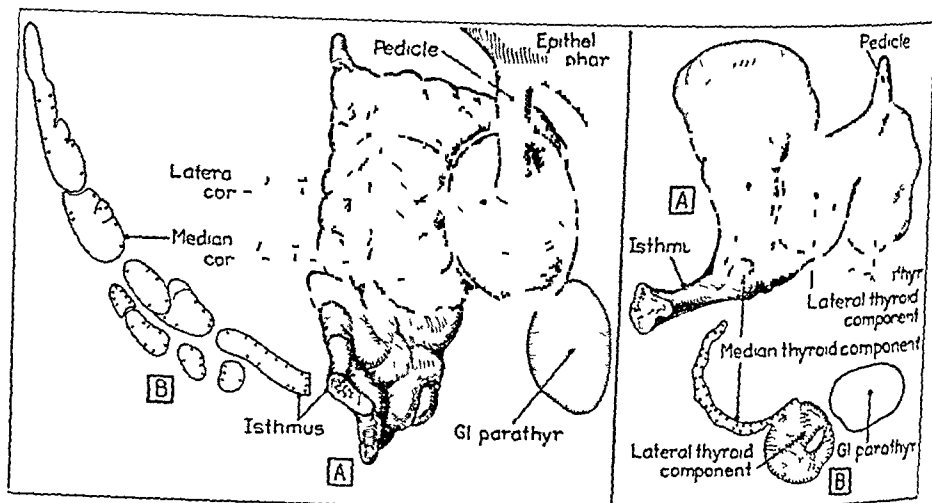


Figure 2

Figure 3

Fig 2—*A*, median view of the median and lateral thyroid components of a 168 mm fetus. The two structures are intimately approximated, the latter still maintains its rounded shape and is connected by a pedicle with the epithelium of the pharynx. *B*, typical frontal section through the median thyroid component to show the arrangement of the thyroid epithelium. (Copied from Weller, G L, Jr. Development of the Thyroid, Parathyroid and Thymus Glands, Publication 443, Carnegie Institute of Washington, 1933.)

Fig 3—*A*, medial aspect of the right half of the thyroid gland in a 13 mm embryo. The lateral thyroid is no longer connected with the pharynx, but the remains of the pedicle are present. *B*, typical transverse section of the same to show that contact between the median and lateral components is intimate and that the lateral thyroid contains a large central lumen. (Copied from Weller, G L, Jr. Development of the Thyroid, Parathyroid and Thymus Glands, Publication 443, Carnegie Institute of Washington, 1933.)

aberrant thyroid tissue were present. Three of these cases have previously been reported by McGlannan. As in the great majority of the

cases reported in the literature, the clinical diagnosis in most instances was incorrect. The most frequent diagnoses were tuberculosis, lymphosarcoma, Hodgkin's disease and cyst of the branchial cleft. These 20 cases have been reclassified after review of the histories, microscopic sections and ultimate results. The accompanying table shows the grouping in the reclassification.

A priori, the presence of thyroid tissue in nonindigenous areas is dependent on the growth of cells misplaced during embryonic development or on cells which have metastasized from a tumor developing at the site of such an island of cells or from a tumor originating within the thyroid gland.

Among the problems which arise in connection with the study of these tumors are their origin, cellular propensities, histologic structure,

Classification of Tumors

Group 1	Adenocarcinoma of thyroid with metastasis to cervical lymph nodes (7 cases)
A	Palpable tumor of thyroid gland on examination 6 cases
B	History of excision of a tumor from thyroid gland 1 case
Group 2	Aberrant malignant thyroid tumor in the presence of a normal thyroid (9 cases)
A	No metastasis to cervical lymph nodes 1 case
B	Metastasis to cervical lymph nodes 5 cases
C	Metastasis to cervical lymph nodes (no known thyroid or aberrant tumor in history or on examination), 3 cases
Group 3	Benign aberrant thyroid tumors (4 cases)
A	Palpable tumor of the thyroid 1 case
B	History of excision of tumor from thyroid, 1 case
C	No palpable tumor of thyroid or history of excision of tumor of thyroid 2 cases

classification, treatment and prognosis. Metastatic papillary adenocarcinoma in the cervical lymph nodes from adenocarcinoma primary either within the thyroid gland or in aberrant thyroid tissue has frequently been mistaken clinically and even histologically for benign hyperplastic aberrant thyroid tissue or benign papillary adenoma.

ANALYSIS OF CASES

Group 1 A (6 cases)—In each instance there was a palpable tumor of the thyroid gland at the time of examination, and in 5 instances the tumor was a typical papillary adenocarcinoma. The remaining tumor was classified as a variant of the papillary adenocarcinoma and showed marked vascular invasion, belonging to the group recently described by Graham. The absence of any evidence of remote metastasis in 5 cases many years after involvement of the regional lymphatic nodes confirms the low grade of malignancy of the majority of these tumors.

One patient returned with regional recurrence in the supraclavicular area three and a half years after excision of a small nodule in the thyroid gland and a group of cervical lymph nodes and has since been lost from observation. Another is free from evidence of metastasis eighteen years after the appearance of the tumor in the thyroid gland and sixteen years after excision of the tumor and a cervical lymph node which was the seat of metastasis. A third patient died of "cancer of the thyroid" thirty-



Fig 4—Low power photomicrograph of a low grade papillary adenocarcinoma of the thyroid gland. In 1906, after being apparent for fourteen years, this tumor was excised with a group of cervical lymph nodes involved by metastasis. The patient died in 1929, twenty-three years after operation, of "cancer of the thyroid."

seven years after onset of the disease and twenty-three years after excision of the thyroid tumor and a group of the cervical lymph nodes (fig 4). One patient (fig 5) was living, with extensive involvement of the thyroid and cervical lymph nodes when last heard from, in 1935, ten

years after a biopsy which showed papillary adenocarcinoma. One patient returned for excision of the right lobe of the thyroid seventeen years after onset of the tumor and ten years after excision of the left lobe and the cervical lymph nodes on the left and has since been lost from observation. The remaining patient (fig 6) in this group, whose

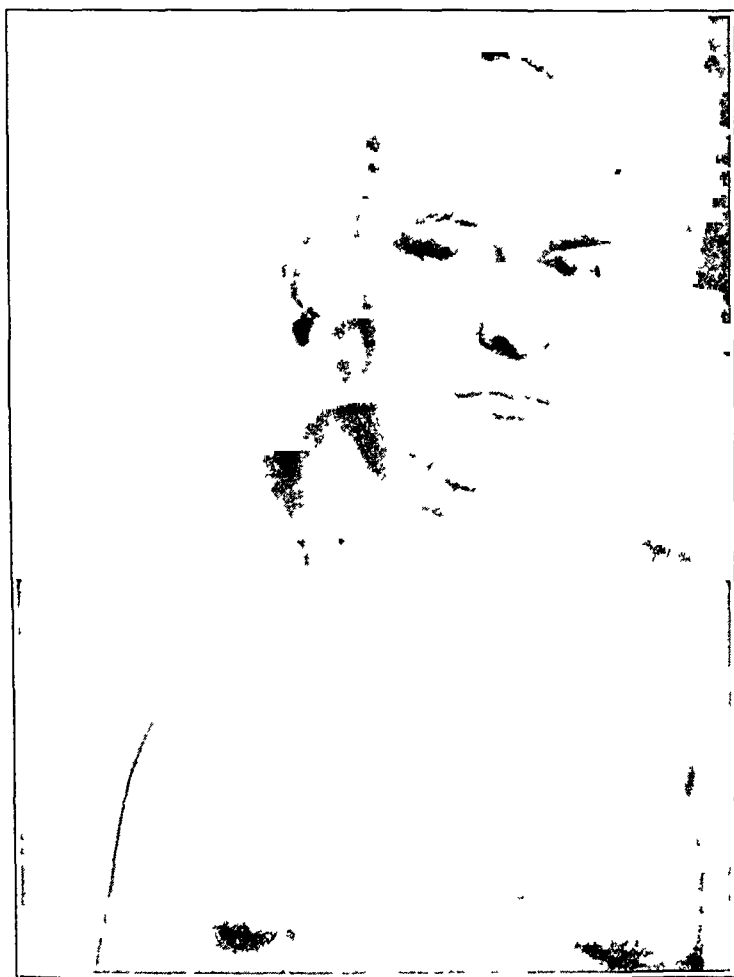


Fig 5—Photograph of a patient taken Jan 10, 1935, ten years after a biopsy which showed papillary adenocarcinoma.

lesion was classified as a variant, died nine years and eight months after the tumor was first observed and four years and eight months after operation. At autopsy metastases were observed in the brain, lung, spleen and small intestine. The age at onset in this group varied from 18 to 46 years. Four of the 6 patients were under 35 years of age, and the average age at which the tumors became apparent was 36 years. Two of the patients had slight toxic symptoms.

Group 1 B (1 Case) —The sections in this case showed chiefly colloid and fetal adenoma with areas of papillary adenocarcinoma. Thyroidectomy was performed at the age of 38. Subsequently there were three operations for excision of the cervical lymph nodes. The patient died eighteen years after the thyroidectomy, with inoperable local recur-



Fig. 6—Low power photomicrograph showing a variant of papillary adenocarcinoma of the thyroid gland. Note the vascular invasion. The patient died nine years and eight months after the tumor was first observed and four years and eight months after it was excised. At autopsy metastases were observed in the brain, lung, spleen and small intestine.

rences involving the pharynx and esophagus and producing gradual starvation. There was no clinical evidence of remote metastasis. Autopsy was not performed.

Group 2 A (1 Case) —The patient was a Negress 39 years of age. There was a small, rounded firm nodule 1.5 cm. in diameter to the left of the midline of the neck and below the hyoid bone. This nodule had been present for one year when it was excised (Dec. 8, 1936). The sections showed colloid and fetal adenoma and the early stage of papillary adenocarcinoma. The patient was reported well in August 1938. In view of

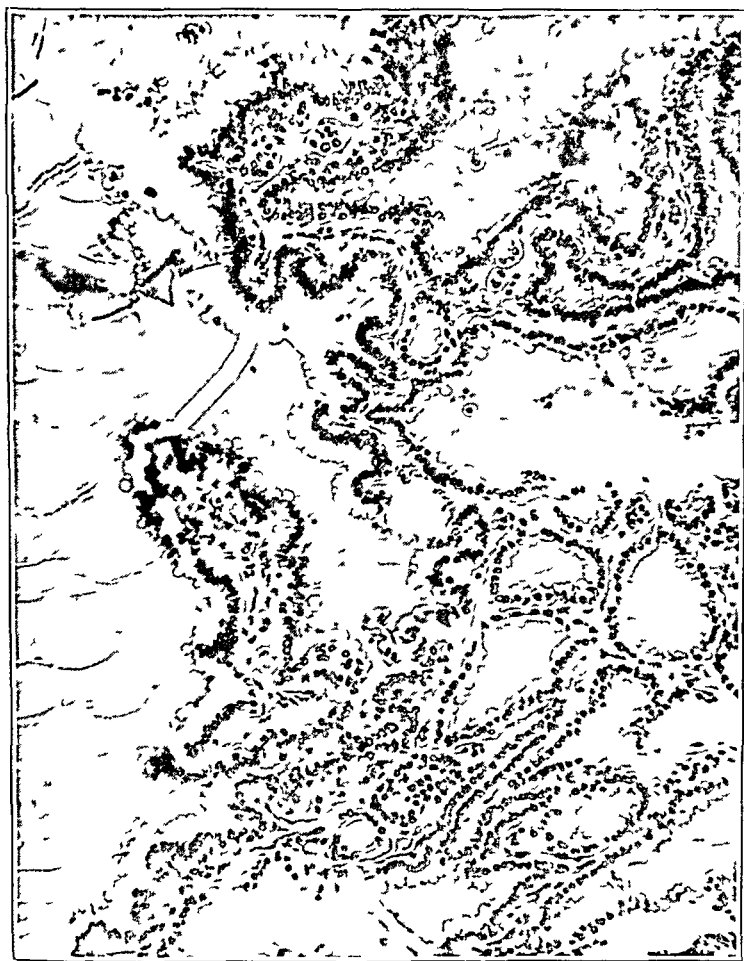


Fig. 7—Low power photomicrograph of the early stage of papillary adenocarcinoma. (See text for clinical note.)

the benign nature of the larger part of the tumor and the very early stage of adenocarcinoma, it is possible that the restricted operation may have been sufficient to prevent recurrence.

Group 2 B (5 Cases) —The histologic structure in 4 of these cases was that of typical papillary adenocarcinoma similar in appearance to the tumors in group 1. In 1 of these there was, in addition, grade 4

carcinoma In the remaining case the microscopic picture was that of colloid adenoma with invasion of the blood vessels as described by Graham The patient died of metastasis twelve years after onset of the disease, during which time there were five operations and roentgen and radium therapy were given Two of the patients are well eleven years and six years respectively after onset of the disease and five years and two



Fig 8—Low power photomicrograph showing a typical papillary adenocarcinoma

years respectively after operation One patient has been lost from observation The patient with a combination of papillary adenocarcinoma and grade 4 carcinoma died six and a half years after onset of the disease and six months after operation (figs 8 and 9)

The thyroid gland in each case in this group was considered normal, and in no instance was there any nodule within the thyroid gland or any toxic symptoms The age at which the tumor became apparent varied

from 22 to 69 years, and the average age was over 47 years, higher than in group 1 A

Group 2 C (3 Cases) —The 3 cases in this group differed clinically from the cases in group 1 by the absence of any tumor in the thyroid gland and from the cases in groups 2 A and 2 B by the absence of any demonstrable primary aberrant thyroid tumor. In none were toxic symp-

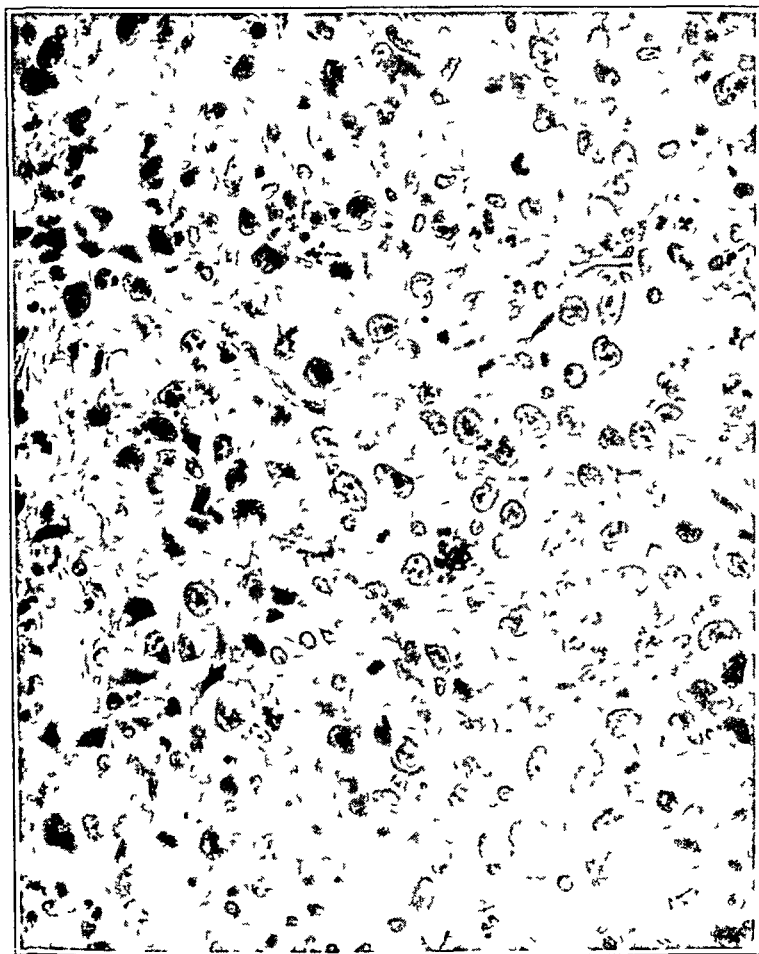


Fig 9—High power photomicrograph from another area in the same tumor, showing highly malignant anaplastic carcinoma

toms present. In 2 of the cases there had been a previous incomplete operation.

Because the microscopic pathologic picture in each of these 3 cases was that of papillary adenocarcinoma similar to the papillary adenocarcinoma in groups 1, 2 A and 2 B it seems likely that the primary tumor either was excised at a previous operation or was so involved in the mass

of carcinomatous lymph nodes that it was indistinguishable from them. The ages at which the tumor became apparent were 18 years, 8 years and 28 years respectively, and the duration of the tumor prior to operation was six years, thirty years and two years respectively. Attention is called to the youth of the patients at the time the tumor first appeared and the long duration of the tumor without evidence of extension beyond the regional lymph nodes.

HISTOLOGIC DESCRIPTION OF PAPILLARY ADENOCARCINOMA

The primary aberrant tumor may indicate its origin from a thyroid primordium when it is composed of large coalescent colloid-containing vesicles lined by cuboidal epithelium showing an early stage of papillary proliferation (fig 7). This is true even in the advanced stage of a very cellular anaplastic carcinoma containing tumor giant cells and showing almost complete absence of stroma when this is continuous with an area of papillary adenocarcinoma (figs 8 and 9).

Sometimes the tumor is made up of large lobules of irregularly dilated and coalescing vesicles in which there are no remains of colloid material, united by a scanty amount of loose connective tissue and separated by dense fibrous stroma. The acini are lined by a single layer of cuboidal or columnar epithelial cells, and there is scarcely any papillary proliferation, the tendency being toward formation of increasing numbers of small acini. Vascularity is only moderate, and calcification is not present. Where the lobules become more irregular, the loose intralobular stroma disappears and the picture is that of a syncytium with epithelium-lined spaces (fig 10). Where all evidence of lobules disappears, there is dense connective tissue infiltrated at intervals by epithelial cells differentiating into glandlike structures and producing the typical appearance of an adenocarcinoma.

The microscopic appearance of papillary adenocarcinoma originating in the thyroid gland or in aberrant thyroid tissue is most typical when observed in a cervical lymph node showing metastases from such a tumor¹. As a rule the normal structure of the lymph node is destroyed, and variable amounts of lymphoid tissue remain. Sometimes at the site of the lymph node there is a diffuse multilocular papillomatous cyst. The wall of the cyst is lined by a single layer of cuboidal or columnar epithelial cells and divided by many thin partitions lined on each side by a layer of similar cells. Between the opposing bases of these epithelial cells is a narrow zone of loose fibrous stroma in width only about twice the height of the lining epithelium except where distended capillaries are present. Projecting into the lumens of the cystic areas are hundreds

1 See figure 13 in Cohn

of small and larger papillomas covered by a single layer of epithelium similar to the epithelium of the cyst wall. These papillomas are usually long and narrow, show marked arborization and contain only enough stroma to support the extensive capillary network nourishing the epithelial cells on the surface. Frequently in the walls of these cystic areas there are large collections of regular colloid-containing vesicles, occasionally

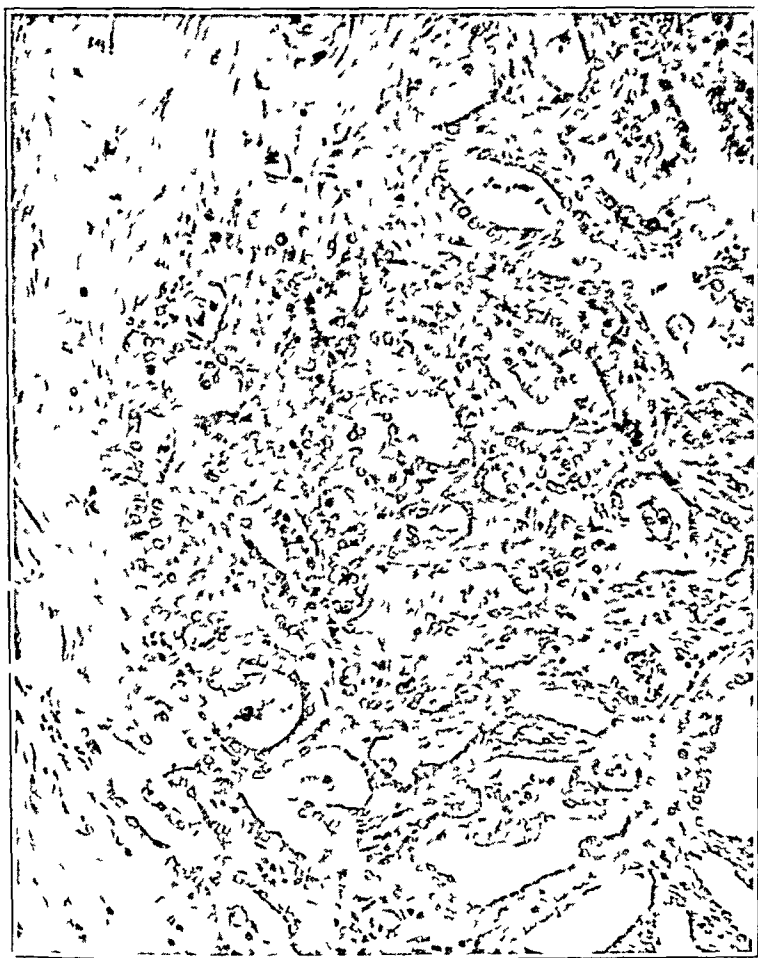


Fig 10—Low power photomicrograph of a primary "lateral aberrant thyroid adenocarcinoma." Note the absence of papillary proliferation.

such vesicles are present even in the papilloma, and sometimes the cysts have a colloid content.

In rarer instances, diffuse areas of colloid vesicles predominate and there are only occasional areas of papillary adenocarcinoma. The tissue is all very vascular, and in addition to the distended capillaries in the walls of the cystic areas and in the stalks of the papillomas there is usually

follow 1 patient since the operation. Six patients are well eighteen years, five years, three years, two and one-half years, two years and one year respectively after operation. These results parallel to some extent those in the larger group recently reported by Crile. The absence of remote metastasis in the pure papillary tumors has led this author to the conclusions mentioned earlier in this paper.

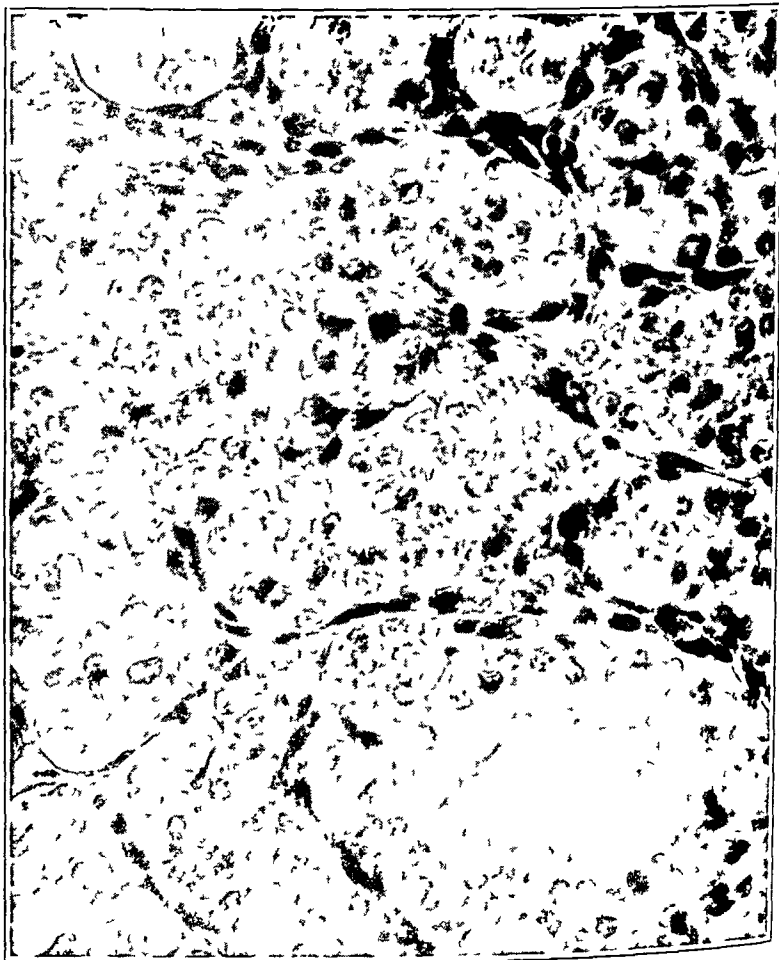


Fig 12—High power photomicrograph of a "lateral aberrant thyroid tumor," showing adenomatous hyperplasia. The growth was excised March 20, 1936. An adenoma had been excised from the thyroid gland Sept 9, 1933. The patient was well July 22, 1939. Compare with figure 11.

COMMENT

If the conclusion of Weller that the definitive thyroid gland is derived from three primordia is correct, it seems logical to conclude that lateral aberrant thyroid tissue and the tumors to which it gives rise are derived from the lateral thyroid component. The histologic appearances of papillary adenocarcinoma arising in the thyroid gland and of papillar

adenocarcinoma arising in lateral aberrant thyroid tissue are so similar that their origin from a common anlage is suggested. If this is so, the location of the tumor within or outside the thyroid would be determined by the time the embryonic tumor cells are split off from the lateral primordium. If the split occurs during fusion of the lateral and median thyroid primordia, the tumor will be located in the thyroid gland, if the split occurs before fusion, the tumor will appear lateral to the thyroid

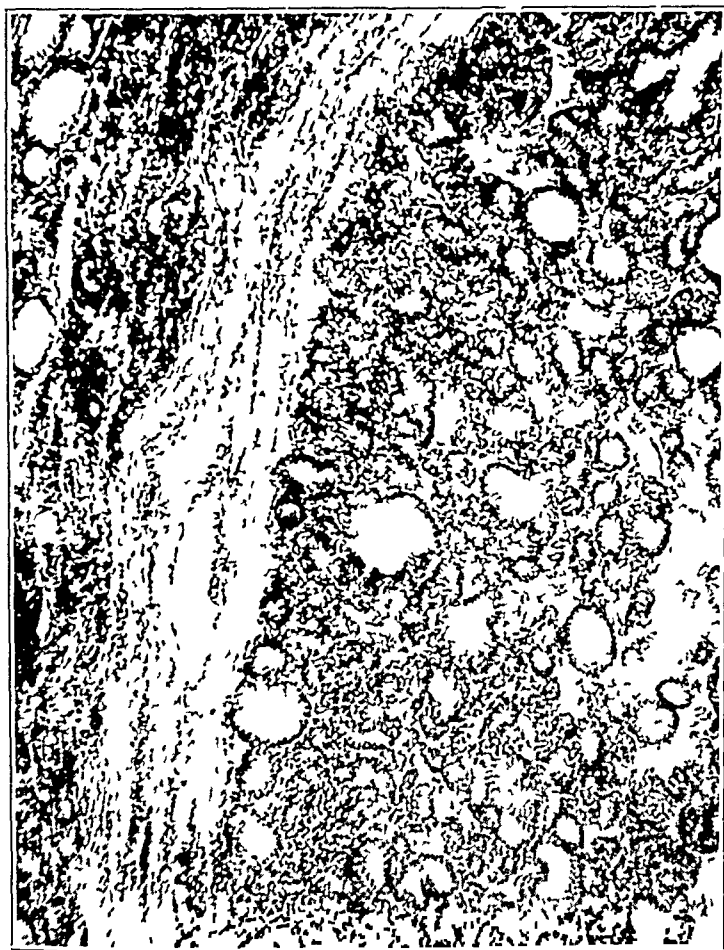


Fig 13—Low power photomicrograph of an encapsulated adenoma of lateral aberrant thyroid tissue (See text for clinical note)

gland as an “aberrant thyroid tumor.” Tending to confirm this theory of the histogenesis of papillary adenocarcinoma is the fact that rarely, if ever, do papillary tumors occur along the tract of the median primordium, whereas papillary tumors are reported to constitute 70 per cent of the “lateral aberrant thyroid tumors” studied by Billings and Paul and composed 80 per cent of the tumors under consideration in this study.

It is true that myxedema has been more frequent after excision of a medial lingual thyroid, but this has also occurred after excision of a lateral aberrant thyroid. Such a case was reported by Probst and Agress.

Group 3 A (1 Case) —The patient was a white man 22 years of age with two small nodules attached to the thyroid gland, a small mass over the trachea and multiple larger masses on the right side of the neck,



Fig 14—Low power photomicrograph of simple colloid hypertrophy in lateral aberrant thyroid tissue. (See text for clinical note)

described as at least 3 cm in diameter. The nodules extended from the submaxillary area behind the sternocleidomastoid muscle to the clavicle. They were of twelve years' duration, and they were associated with toxic symptoms referable to the thyroid. The patient is reported well April 26, 1939, thirty-nine years after onset of the lesion and twenty-nine years after excision of the nodule in the thyroid gland and the lateral nodules.

The microscopic picture showed cystic thyroid acini and solid thyroid acini plugged by epithelial cells showing hyperplasia. There were no areas with papillary arrangement or vascular invasion (fig 11).

Group 3 B (1 Case) —A girl had undergone an operation for excision of a nodular growth from the left lobe of the thyroid when 12 years of age and excision of a nodule from the left side of the neck two years and six months later. The sections from both nodules showed solid acini of hyperplastic thyroid (fig 12). At examination on July 22, 1939, three years and four months after the second operation, we were unable to palpate any new nodules. During the past year the basal metabolic rate has varied from -13 to -32 per cent. The patient is taking thyroid extract. The diagnosis of a benign lesion is based on the histologic appearance of the hyperplasia and the absence of both papillary arrangement and vascular invasion, a picture similar to that in the preceding case, in which the ultimate result is known after a long period of years. In both the nodules were probably the result of compensatory hyperplasia because of a hypoplastic thyroid gland, the second nodule developing in lateral aberrant thyroid cells after excision of one lobe of the thyroid gland.

Group 3 C (2 Cases) —The first patient was a white woman 62 years of age. The tumor, which was 1.5 cm. in diameter, was situated to the right of the larynx about the level of the coracoid process. It had been noticed by the patient for only two weeks, and there were no toxic symptoms. After the excision she lived for twenty-two years. She died at the age of 84 without any evidence of recurrence of metastasis. The microscopic section shows an encapsulated adenoma with hyperplasia (fig 13).

The second patient in this group was a white woman aged 38 with a nodule in the upper right cervical region. It had been present for one and one-half years when it was excised (in 1915). There had been nervousness for one year. The thyroid gland appeared normal. Histologically the lesion showed simple colloid hypertrophy without hyperplasia, papilloma or vascular invasion. There has been no recurrence in the twenty-four years which have elapsed since the operation.

COMMENT

Aberrant thyroid tissue may undergo hypertrophy or even compensatory hyperplasia because of a hypofunctioning thyroid gland or because of neoplasia. In the case of simple hypertrophy the diagnosis can be made with relative assurance. Physiologic hyperplasia, however, creates a diagnostic problem because of the difficulty in distinguishing histologically between hyperplasia and neoplasia in thyroid tissue located outside the capsule of the thyroid gland. When the occurrence of this hyperplastic thyroid tissue beyond the confines of the thyroid gland

follows excision of hyperplastic tissue from within the thyroid gland, as in 1 of the cases aforementioned, the diagnosis is rendered even more difficult. The absence of papillary proliferation and vascular invasion suggests a benign lesion.

SUMMARY

A brief review is made of the literature on tumors of lateral aberrant thyroid tissue.

Twenty cases of thyroid tumors in the lateral regions of the neck with and without an analogous tumor in the thyroid gland have been analyzed and an attempt made to correlate them on an embryologic basis.

Eighty per cent of the patients had papillary tumors, and 3 of these showed, in addition, higher grades of malignancy.

A histologic description of the papillary tumors is given.

Local or regional recurrence after incomplete operation occurred in 71 per cent of the cases of papillary tumor, but none of the patients with pure papillary tumors died of remote metastasis.

Four, or 20 per cent, of the tumors showed benign hypertrophy or hyperplasia of lateral aberrant thyroid tissue, and in this group there has been no recurrence or metastasis during the many years 3 of them have been followed or for more than three years in the more recent case.

CONCLUSIONS

Surgical treatment of papillary tumors in the lateral regions of the neck should consist of their complete excision and block dissection of the cervical lymph nodes. When the lateral thyroid tumor shows no evidence of papillary proliferation or vascular invasion, restricted surgical excision is adequate.

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RELATION OF TUMORS OF LATERAL ABERRANT THYROID TISSUE TO MALIGNANT DISEASE OF THE THYROID GLAND

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SAN FRANCISCO

Tumors of lateral aberrant thyroid tissue offer a particularly fruitful field for the investigator interested in the origins of cancer. In some of the earliest reports of this condition, Hinterstoisser¹ pointed out that the tendency to malignant degeneration in these primarily benign tumors is great. When one considers the fact that the dividing line between innocent and malignant tumors is nowhere less sharply drawn than in tumors of thyroid tissue showing the papillary design, it will be seen that intriguing opportunities are offered in the study of this group of neoplasms. Most investigators agree as to the possibility of malignant change, but there is considerable difference of opinion as to the point at which malignancy begins, the criteria of malignancy and the degree of malignancy, once the diagnosis is established. Dunhill² wrote "It would seem that these misplaced bits of tissue, whether in the lateral triangle of the neck or in the thyroid gland itself, foredoom the host to carcinoma from before the day of birth." On the other hand, Crile³ said "Tumors arising in lateral aberrant thyroid tissue are essentially benign" and "It has not been proven that either distant or local metastasis occurs from papillary tumors of lateral aberrant thyroid origin." These two views represent the extremes, and it is probable that the truth lies somewhere between them.

Because this point of benignancy or malignancy is so controversial, I present 15 cases of tumors of aberrant thyroid tissue. Twelve of the growths I consider malignant, and 3, benign. For each case a short discussion is presented, detailing the reasons for classifying the growth as benign or malignant. Many may not agree with my conclusions after

From the Department of Surgery, University of California Medical School
Read before the Surgical Section of the Third International Cancer Congress,
Atlantic City, N J, Sept 13, 1939

1 Hinterstoisser, H. Beiträge zur Lehre vom Nebenkropf, Wien Klin Wchnschr 1 651-653, 680-682 and 701-703, 1888

2 Dunhill, T P. Carcinoma of the Thyroid Gland, Brit J Surg 19 83-113, 1931

3 Crile, G W, Jr. Papillary Tumors of Thyroid and Lateral Aberrant Thyroid Origin, Surg, Gynec & Obst 69 39-47, 1939

studying the case histories and the photomicrographs. It is evident that in many of these cases only the passage of time and the eventual outcome will prove whether the tumors are malignant (as in case 3, cited here). Because these tumors of aberrant tissue are of such a low degree of malignancy and because many malignant tumors of thyroid tissue in general have a tendency to lie dormant or to progress very slowly over

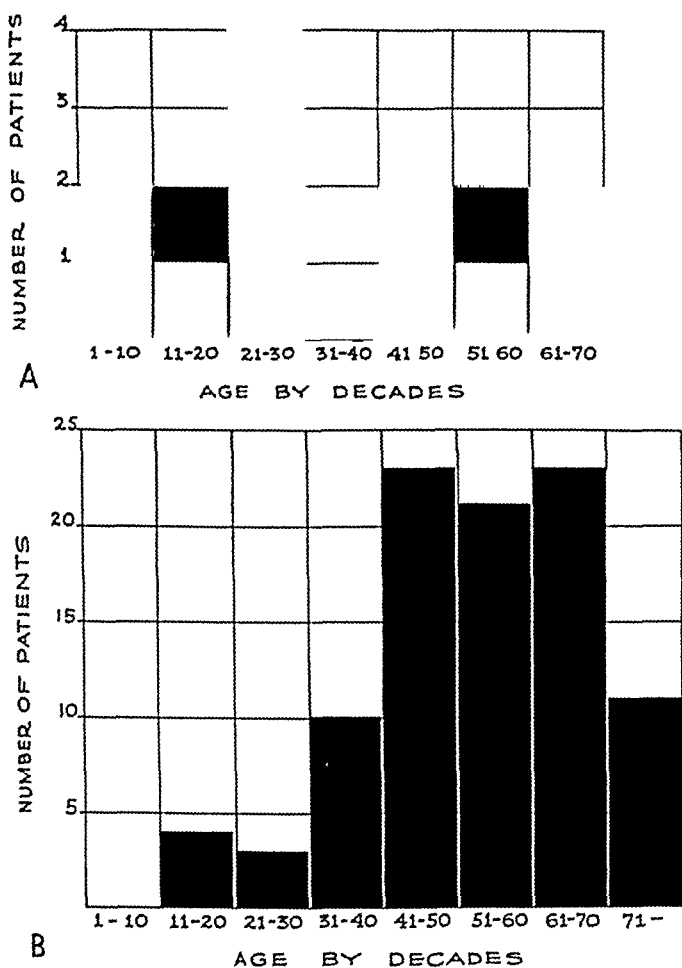


Fig 1—A, age incidence of malignant tumors of lateral aberrant thyroid tissue. B, age incidence of 95 malignant goiters not of lateral origin.

many years, a long period of observation in addition to a rigid follow-up in all cases is an absolute necessity before conclusions can be drawn. I hesitate to draw absolute conclusions even if a follow-up has been obtained on each patient to the time of his death or, if he is living, to the time of writing, as has been done in these 15 cases of tumor of aberrant thyroid tissue and in 95 cases of cancer of the normally placed thyroid gland.

COMPARISON OF LATERAL AND MIDLINE NEOPLASMS

In 4,274 operations from which material was available for pathologic examination there were 15 tumors of lateral aberrant thyroid tissue and 95 malignant growths arising in normally situated thyroid glands. This gives a ratio of 1 to 285 for the former and 1 to 45 for the latter. The average age of the 12 patients with malignant tumor of a lateral aberrant thyroid was 24, of the 95 with malignant tumors in the midline, 52.7, and of the 3 with lateral benign tumors, 48. Fifty-eight per cent of the patients with malignant tumor arising in lateral aberrant thyroids were under 30 years of age, while only 7 per cent of malignant tumors of the midline appeared in the first three decades of life. The comparative statistics for age are shown in the accompanying graphs (fig. 1). The early onset lends weight to the assumption that tumors of lateral aberrant thyroid tissue are associated with developmental abnormalities, such as lack of fusion of the median and the lateral thyroid anlagen. They further suggest that the tumors are not primarily malignant, since they develop before the age when malignant tumors are prone to appear. In this respect it must be emphasized, however, that general conclusions should not be drawn from a small series, as the oldest patient did not have his tumor till he reached the age of 66 years, and 3 of the 12 patients with malignant tumor of aberrant thyroid tissue were over 51 years of age when they came under observation.

The sex ratio was as follows

	Males	Females	Ratio
Malignant tumors of lateral aberrant thyroid tissue	5	7	1:1.4
Midline malignant tumors	24	71	1:3
Benign tumors of lateral aberrant thyroid tissue	1	2	1:2

In the general series of patients with goiter operated on during the same interval the ratio was 1 male to 7 females in 4,274 operations.

The duration of the tumors before the patients sought medical attention varied from eight months to fifteen years, the average being fifty-six months (table 1). An analysis of the histories indicates that

TABLE 1—*Probative Duration of Tumor and Probable Duration of Malignancy*

Case	Duration of Tumor	Probable Duration of Malignancy
1	6 years*	1 year
2	15 years	3 months
3	16 months	16 months
4	2 years	1 year
5	6 years	8 months
6	8 months	8 months*
7	2 years	2 years*
8	11 months	2.4 months
9	15 years	Unknown
10	3 years	1 year
11	15 months	15 months
12	25 years	6 months*

* Midline tumor of six years' duration before operation. A lateral nodule appeared six years after operation and was removed one year later.

4 of the tumors were malignant from the onset (cases 3, 6, 7 and 11). In 1 case (9), a "midline and lateral" tumor had grown for eight years and had remained unchanged for six, so that no estimate of the duration of malignancy could be made. In the remaining 7 cases a midline or a lateral tumor had been in existence for from one to fifteen years before rapid growth or the appearance of other nodules suggested malignant change. It should be realized, however, that the onset of rapid growth is not a dependable sign of malignant change, as many of these tumors, malignant from the beginning, either lie dormant or grow slowly for years, on the other hand, rapid and continuous growth may take place in tumors which run a clinically benign course and show little, if any, evidence of malignancy in their microscopic pattern.

A comparison of the mortality for tumors in the two locations is of interest

	Lateral Malignant	Midline Malignant	Lateral Benign
Dead of disease	3 (25%)	31 (53.5%)	0
Living with recurrence or persistence of disease	4 (33%)	10 (10.5%)	2 (66%)
Living without evidence of disease	5 (42%)	29 (50.5%)	1 (33%)
Dead of intercurrent disease	0	5 (5.5%)	0

Of the 3 patients dead of lateral tumors, 2 (cases 3 and 5) had growths of the papillary type, while 1 (case 9) had a tumor of the malignant adenoma type. Of the 12 malignant tumors of lateral aberrant tissue, 7 either were predominantly papillary or showed some signs of that type of growth, while 5 showed no tendency toward papilliferous change.

LOCATION OF TUMORS

The most common location of lateral aberrant tumors is along the course of the sternocleidomastoid muscles. Figure 2 and table 2 show the distribution of the tumors in my 15 cases. It is worthy of note that in only 3 instances were the tumors single, that the most common site was under the middle of the left sternocleidomastoid muscle, that 42 of them were located in the left side of the neck and 29 in the right, and that in only 3 cases was there no associated involvement of the thyroid gland.

REPORT OF CASES

CASE 1—E. B., a white woman 29 years of age, first consulted me Feb. 24, 1924, complaining of swelling in the left side of the neck for the past five or six years. She had experienced a feeling of tightness and of dull, aching pain, persistent and increasing for the past two or three years. On physical examination a fairly hard, rounded mobile nodule could be felt in the left upper pole of the thyroid gland.

At operation, on February 25, an encapsulated nodule was removed from the left upper pole of the gland, and a smaller nodule, showing questionable erosion of the capsule, was removed from the right upper pole.

The pathologic report was in part as follows Both the large mass (that on the left) and the smaller one showed mostly the papillary cystadenoma type of tissue One area in the smaller mass showed active sheets of invading tissue A pathologic diagnosis of early malignant tumor arising in an adenoma was made (fig 3)

The patient was kept under observation, and on April 30, 1930, lateral nodules were noted along the anterior border of the left sternocleidomastoid muscle, just below the angle of the jaw One measuring 27 cm in diameter was noted above the left clavicle These were removed on March 23, 1931 and were found to be deep and adherent to the carotid artery and the jugular vein One was ruptured on removal, with release of thick, grayish necrotic material On pathologic examination the tissue was called metastatic, slowly growing carcinoma, identical with the tumor from the original goiter No lymph node architecture was noted During March 1931 the patient received roentgen therapy to the amount of 1,700 roentgen units

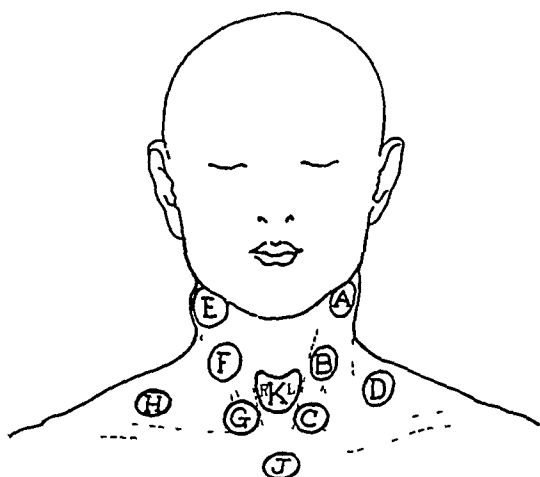


Fig 2—Diagram showing the most common locations of lateral aberrant tumors Table 2 gives the location of the tumors in our 15 cases in reference to this diagram

TABLE 2—Location of Tumors

Location	Case															Total	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Tumors	Patients
A	1			1	1	1				1	1	1	2			9	8
B	1		1	2	1	1				2	2	3	3	1	1	18	11
O	3		1		1	4				1	1	1	1			13	8
D				1	1											2	2
E					1		2				3					6	3
F		*			1	3	1				4					10	5
G		1			1	1	3	1			2					9	6
H					1				2		1					4	3
J					1											2	2
KL	*		1	*	1	2				1	*		*	*		9	9
LR	*	*			1		*		1		*					6	6
Total tumors per case	7	1	2	5	11	12	7	1	3	5	16	6	7	2	1	89	

* Indicates involvement of area by tumor listed under another location

In March 1932 a new group of nodules was noted She was given a further course of therapy, 650 roentgen units, with little resultant change By March 29, 1934 the nodules were slightly larger, and operative removal was advised

On April 15 nodules were noted along the left sternocleidomastoid muscle and above the left clavicle. These were removed through separate incisions on April 16. All were adjacent to the jugular vein but not invading it. The lower ones were matted together and removed en bloc. Seven grams of tissue was excised. The nodules were hard, elastic and bluish gray. Microscopic examination showed that they were not lymph nodes but encapsulated thyroid tissue. They were entirely similar to those observed at the two previous operations. On pathologic examination the tissue was diagnosed as lateral aberrant thyroid adenoma.

There was no sign of recurrence by May 15, 1939, when the patient was last examined.

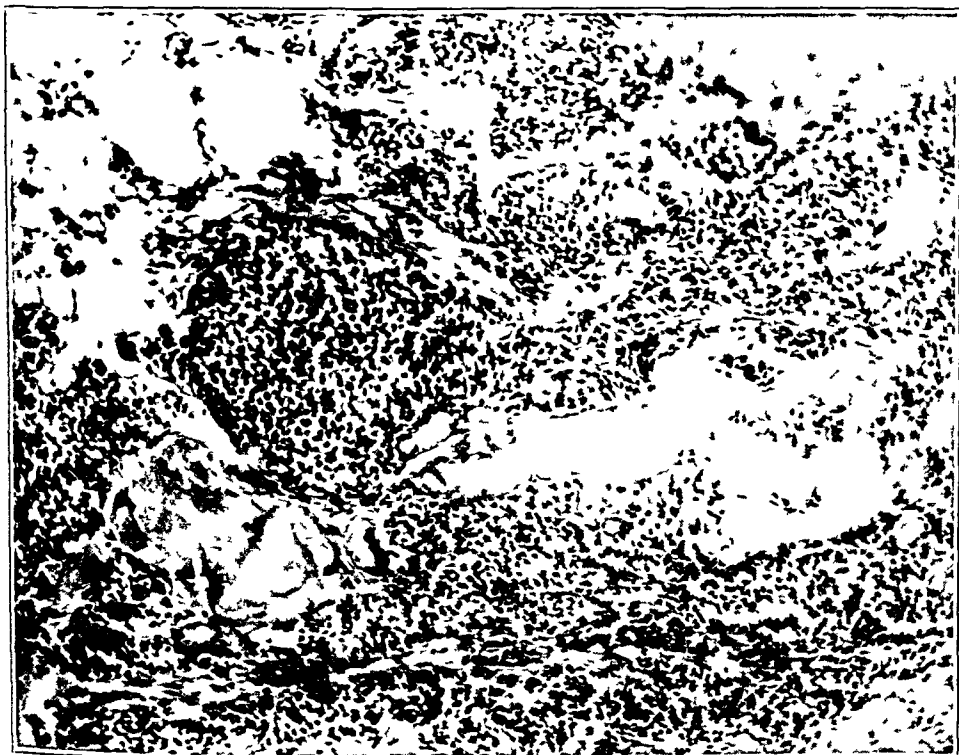


Fig 3 (case 1) —Photomicrograph ($\times 120$) of tissue removed from E. B. at the first operation. The clear areas represent hyalinized alveoli which are surrounded by small epithelial cells in patternless fields. A similar picture was seen in all subsequently removed tissue.

Comment—The growth in this case was originally placed among the malignant tumors of the normally placed thyroid gland because of the erosion of the tumor capsule observed at operation and grossly on pathologic examination. The microscopic picture lent evidence to a diagnosis of malignant tumor, although the malignancy was of low degree. The appearance of lateral nodules six years and ten years after the original operation lent further weight to this presumption. There was no gross or microscopic evidence that these recurrences were

metastases to lymph nodes, but a study of the microscopic sections showed a picture similar to that of the original tumor, and there was evidence of penetration of the blood vessels in both the original and the recurrent tumor. Against the diagnosis of malignant tumor were the absence of mitosis in all specimens and the fact that the patient has

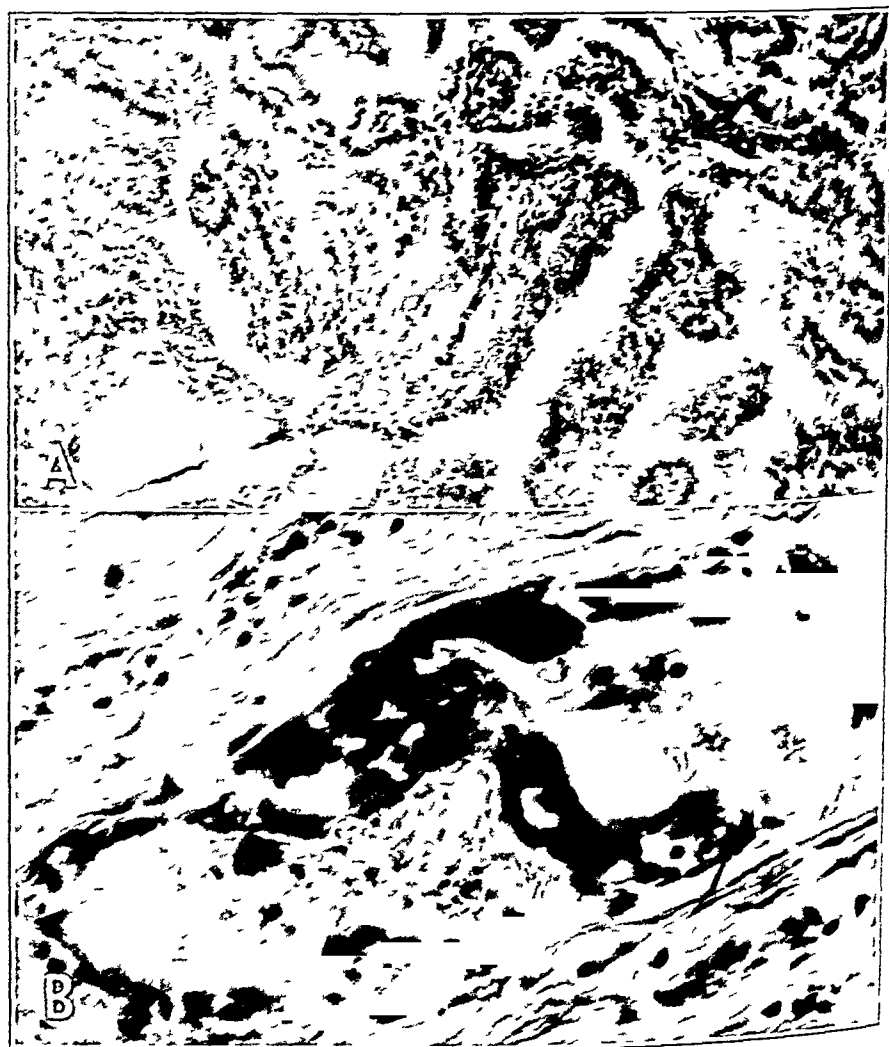


Fig 4 (case 2) —Photomicrographs of tissue removed from M. S. A, specimen ($\times 120$) from the interior of the tumor, showing the usual papillary pattern. B, specimen ($\times 450$), showing invasion by carcinoma of the blood vessels in the muscular tissue adjacent to the tumor.

remained well, without signs of local recurrence or generalized metastases for five years since the last operation, without radiation therapy.

CASE 2—M. S., a white woman 63 years of age was first seen April 16, 1921 with a painless, slowly growing tumor on the right side of the neck, just above the

clavicle, which had been present fifteen years. It had grown rapidly during the three years preceding my examination of the patient and had doubled in size. It had been firm until four months earlier, when it had become soft and fluctuant. The patient stated that the lump started near the midline, below the cricoid cartilage, and extended laterally and upward to the angle of the jaw. It had become lobulate one year previously. The tumor produced no symptoms.

On physical examination a large lobulated mass could be seen and felt, apparently superficial to the right sternocleidomastoid muscle and extending from the suprasternal notch upward toward the angle of the jaw. It was only slightly movable and apparently was attached to the underlying structures. Although it moved slightly with deglutition, it did not seem to be attached to the thyroid gland. It was hard in some areas and soft in others.

At operation, on April 22, the mass was found to be made up of multiple cystic and solid tumors adherent to the neurovascular bundle but pushing the sternocleidomastoid muscle laterally and back. It extended medially, obliterating the ribbon muscles, and was attached to the right lobe of the thyroid by a pedicle.

On pathologic examination a diagnosis was made of papillary carcinoma, probably arising in lateral thyroid tissue. Invasion of the blood vessels was found in a number of areas (fig. 4).

The patient was living and well in May 1939.

Comment—This case represents one of the apparent paradoxes of cancer of the thyroid. The tumor was grossly malignant in appearance at operation in that it had penetrated the ribbon muscles and spread throughout the neck regardless of cleavage planes. It was grossly and microscopically malignant on pathologic examination in that it had penetrated its capsule, infiltrated muscle and invaded the capsular vessels in many places. There was normal-appearing thyroid tissue in the section, and the malignant areas showed a papillary pattern for the most part, but there were many areas of adenocarcinoma where the tumor was invasive. The photomicrograph (fig. 4 B) showing invasion of the blood vessels was taken from a portion of the specimen some distance outside the tumor capsule and in the midst of skeletal muscle fibers. This patient received no roentgen therapy after operation and yet is living and apparently free of disease over thirteen years later. In this case a question arises as to the origin of the tumor. Although it occupied a position suggestive of lateral aberrant thyroid origin, it was attached to the right lobe of the gland by a small pedicle, and the patient stated that it had first appeared near the cricoid cartilage and progressed lateralward.

CASE 3—E. F., a white woman 62 years of age, first consulted me because of a mass in the left side of the neck on June 15, 1927. The mass had been first noticed in February 1926. It had been unassociated with pain or discomfort and had apparently remained the same size or grown very slowly during the year and a half of its existence. The patient had lost 4 to 8 pounds (1.8 to 3.5 Kg.) in the past six months. Examination gave essentially negative results except for the condition in the neck.

On the left side of the neck there was a large mass, roughly sausage shaped, 14 cm. in length, lying under the left sternocleidomastoid muscle and running

obliquely from the region of the left upper pole of the thyroid gland upward and backward to and immediately beneath the mastoid process. The tumor was sharply outlined, movable and not tender. It was not thought to be connected with the left lobe of the thyroid and did not move with deglutition. There was a second nodule protruding just above the left clavicle, lateral to the lower end of the sternocleidomastoid muscle. A working diagnosis of tuberculous lymphadenitis was made, and a biopsy specimen was removed on June 15.

Pathologic examination of this tissue showed papillary carcinoma of the thyroid. On July 15 the patient was operated on, and a left subtotal lobectomy of the thyroid and radical neck dissection on the left side, including the jugular vein, were carried out. At this time the larger lateral mass was found to be attached to the outside of the left lobe of the thyroid. The smaller nodule, above the clavicle, was separate.



Fig 5 (case 3)—Photograph of E. F., taken in the interval between the recurrences of 1931 and 1938.

After operation, from July to October, the patient received 3,300 roentgen units directed to the left side of the neck, and from Dec. 2 to June 12, 1928 she received an additional 2,200 roentgens. Before the radical operation was carried out, in July 1927, a complete roentgen study of the skull and long bones had shown no metastatic lesions. The patient was followed closely and remained well until December 1931, when a small, tender nodule appeared in the left side of the neck, under the middle of the scar. This disappeared after a course of roentgen therapy in which she received 1,400 roentgens per field. A photograph (fig. 5) taken at this time showed no masses, and examination demonstrated a soft, pliable scar.

In April 1937 she was treated for acute disease of the gallbladder and in eight months of dietary treatment she lost 28 pounds (12.7 Kg.).

In May 1938 Horner's syndrome developed on the left. This was felt to be due to involvement of the cervical portion of the sympathetic nervous system by recurrent carcinoma. At this time some indefinite induration could be felt in the subcutaneous tissues of the left side of the neck. She was given a course of roentgen therapy during August 1938. The treatment was applied to three fields, anterior, posterior and lateral, on the left side, and she received 1,375 roentgens per field. The induration disappeared and Horner's syndrome decreased, apparently as a result of this therapy.

Suddenly, in September 1938, cough, dyspnea, cyanosis and fever developed. These increased in intensity, and the patient died three days later, September 14.

An autopsy was performed, with the following results. No masses were palpable in the neck. The entire laryngeal region was observed to be bound down by old, dense fibrous tissues. The larynx was removed with extreme difficulty, and on its anterior aspect one observed only a small amount of muscle tissue and no thyroid tissue. The right lung was slightly collapsed, the left lung was completely collapsed by the pressure of about 2,000 cc of amber pleural fluid. The visceral and parietal pleura on the left were studded with multiple nodules 5 to 8 mm in diameter. Similar nodules were found deep in the parenchyma of the lung. There was no obstruction of the bronchial tubes, and the compression of the lungs was apparently due to the pleural effusion. Multiple areas of bronchopneumonia were present in both lungs. The remainder of the autopsy observations were of little interest.

Microscopic studies showed a few areas of cellular infiltration in the scar tissue dissected from the larynx. The tumor tissue on the pleural surface (fig 6) showed a compact cellular, undifferentiated type of growth, while that in the parenchyma of the lung resembled the original papillary structure of the tumor removed eleven years earlier.

The pathologist stated that the clinical and autopsy observations suggested that the cancer cells were not completely removed but were held in abeyance by roentgen therapy. The factors stimulating growth after ten years are unknown. The first evidence of active regrowth was the Horner syndrome, which was probably due to pressure of the mass on the neighboring cervical portion of the sympathetic trunk or to actual infiltration of it by tumor. Later there developed an indefinite mass, never large, for there was no demonstrable enlargement at autopsy.

The pulmonary and pleural metastases, judging from their milium size, must have been relatively recent. The cause of death was total collapse of the left lung and partial collapse of the right lung due to effusion. The effusion was undoubtedly due to the tremendous number of pleural metastases.

Comment—It seems to me that this case is significant because it is completed by death and autopsy. It is a typical instance of aberrant papillary thyroid disease and, to a large extent, forms the basis for my determination of malignancy in these cases. In the first place, the microscopic picture (fig 6C) differed little from that of the usual lateral aberrant thyroid tumor, in which one often finds few criteria of malignancy. The great bulk of the tumor showed a papillary design. In some areas, as in most of these tumors, there was a transition to the alveolar pattern, which could be seen invading the capsule and surrounding the thyroid gland and the adjacent lymphoid tissue, but nowhere was

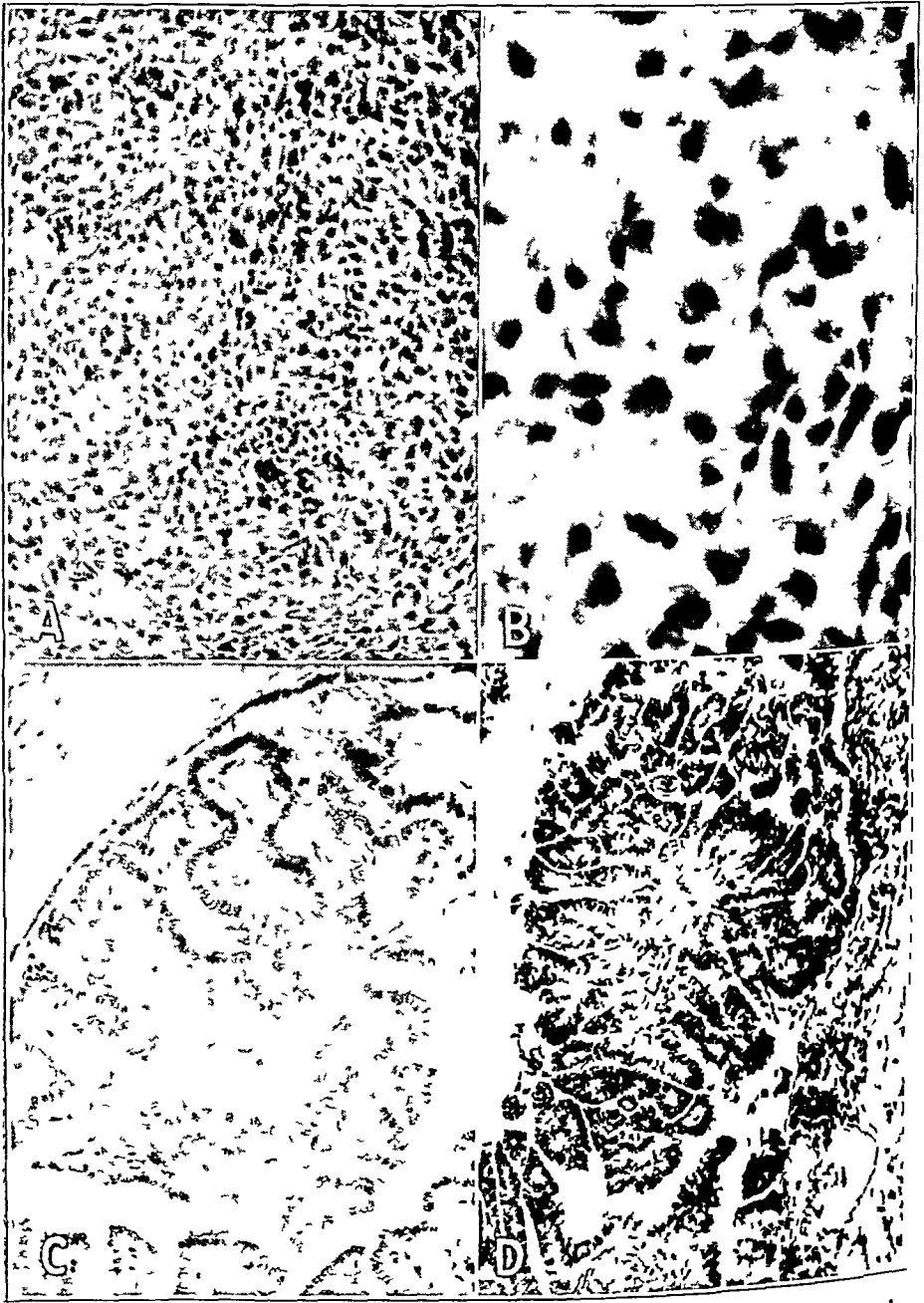


Fig 6 (case 3) —Photomicrographs of tissue removed from E. F. *A*, pleural metastases ($\times 120$), *B*, pleural metastases ($\times 500$), *C*, original tumor ($\times 120$), *D*, papillary pattern assumed by metastases deep in the lung ($\times 120$)

there evidence of invasion of the blood vessels. The patient remained well for four years after resection and irradiation, and when signs of recurrence appeared they were meager and were promptly amenable to roentgen therapy. Seven years then elapsed in which she was seen frequently, and no signs of recurrence were demonstrable. Even at the end of this time, when Horner's syndrome appeared, suggesting a local extension, there was little in the neck to show for it. Again there was a prompt and apparently favorable response to radiation, but it is to be presumed that tumor cells had perforated the left pleural apex or had been carried to the left lung by invasion of the blood stream at the time when the local invasion of the neck seemed to be responding so nicely to therapy. The absence of metastases in the right lung and pleura point to direct extension rather than to extension via the blood stream. It has been my experience that the papillary tumors recur locally and spread by extension, while the malignant adenomas, both of the Langhans type and the more undifferentiated patterns, spread by dissemination through the blood stream.

In the pleural and pulmonary metastases there is an interesting demonstration of the inherent ability of these tumors to change their morphologic characteristics in conformity with their environment. On the pleural surface (fig 6, *A* and *B*), where the tumor grew on a flat surface in a fluid medium, the cells were compact, undifferentiated and patternless, while in the substance of the lung, where pressure was presumably less and a nutritive stroma was present, the tumor reverted to its original papillary form (fig 6 *D*).

That the tumor was malignant is proved by its repeated recurrence and the death of the patient, that the degree of malignancy was low is demonstrated by the long period of survival and the equally long periods of apparent good health between recurrences.

CASE 4—J W, a white girl 16 years of age, first consulted me Sept 24, 1930. Two years earlier she had noted a painless lump the size of a walnut in the left posterior surface of the neck. This had grown slowly until one year previously, when several similar lumps appeared on the left side of the neck and grew rapidly. Two months previously the original walnut-sized nodule had been removed for examination and had been diagnosed as lateral aberrant thyroid tissue.

At the time of my examination of the patient there were three nodules under the left sternocleidomastoid muscle, the highest opposite the angle of the jaw and the largest, about 4 cm in diameter, deep under the center of the muscle. The left lobe of the thyroid gland was enlarged, firm and nodular. On September 25 she was operated on, and a partial right lobectomy and subtotal left lobectomy were performed. Separate masses were removed from along the anterior border of the left sternocleidomastoid muscle (overlying the carotid artery, under the angle of the left jaw). A chain of nodes extending down into the superior mediastinum was also removed.

Pathologic examination of the tissue removed revealed a condition diagnosed as adenocarcinoma involving the left lobe of the thyroid gland and a chain of

lateral aberrant thyroid nodules. The smaller of these lateral nodules showed some peripheral lymphoid elements. One normal, uninvolved lymph node was found attached to the posterior surface of the largest lateral mass.

After operation the patient received roentgen therapy from September 1930 through January 1931, a total of 2,500 roentgen units. On March 23, 1931, one small nodule was present in the region of the left tonsillar lymph node, which gradually decreased until it was no longer palpable by May 14, 1935. The patient has remained well, and when she was last seen, June 15, 1938, almost eight years had elapsed since the operation and more than ten years since the known onset of the disease.

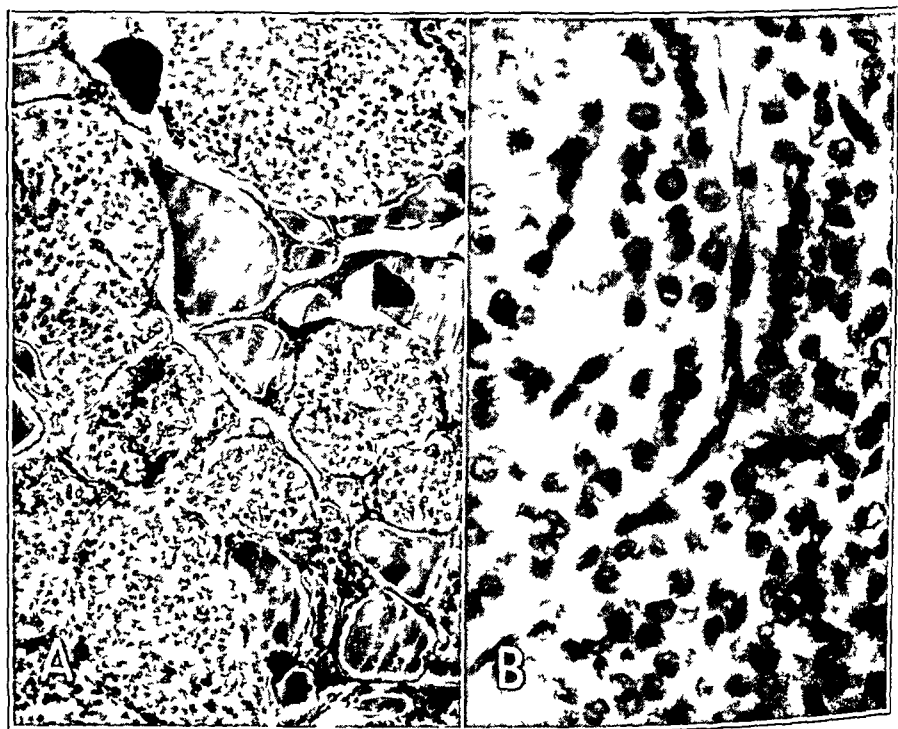


Fig 7 (case 4) —Photomicrographs of tissue removed from J. W. A, $\times 120$, B, $\times 500$. This picture was uniform throughout the lateral and midline nodules.

Comment—This is a most interesting and instructive case. There is no question of the lateral origin of thyroid tissue. It is probably justifiable to assume that the stimulus to its appearance and growth was to be found in an increased demand for thyroid function associated with adolescence. In all specimens removed the same microscopic picture was observed, and nowhere did this show the papilliferous pattern so commonly seen in lateral aberrant thyroid tissue. As the photomicrographs (fig 7) show, the solid cellular areas, typical of the Langhans proliferating adenoma, were invading apparently normal thyroid tissue, or apparently functional areas had appeared in the midst of tumor tissue.

A lymph node removed from behind the largest aberrant mass showed no involvement, while the smaller nodules showed peripheral lymphoid tissue, suggesting that they had been lymph nodes replaced by metastatic growth. Mitotic figures were rare, and no invasion of blood vessels was apparent. This tumor was placed in the malignant group because of the invasive quality of the growth in the left lobe of the thyroid, both grossly and microscopically, and because of microscopic invasion and perforation of the capsule in some of the lateral tumors. Why a nodule

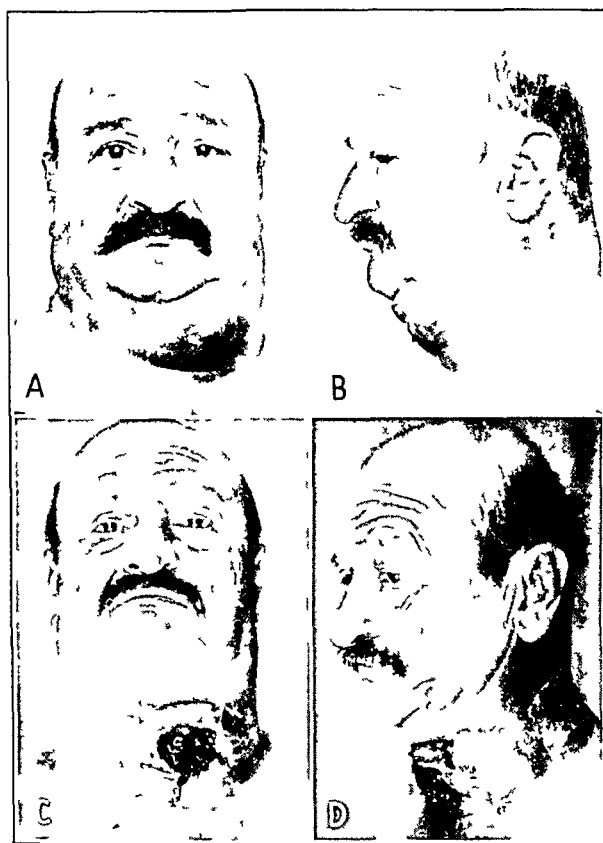


Fig 8 (case 5)—Photographs of the patient. *A* and *B* were taken prior to administration of roentgen therapy, *C* and *D*, approximately two months after roentgen therapy. Note the decrease in bulk of all tissues leaving the lateral nodules, especially those on the right, relatively more prominent.

measuring 2 cm in diameter should become apparent in March 1931 and disappear without treatment in four years I do not know. It suggests that the lateral tumors were benign or that, if malignant, their potentialities for growth were dormant until the proper stimulus was furnished.

CASE 5—J. O., a white man 70 years of age, was first seen in March 1932. He had first noticed, six years previously, a small painless lump, the size of a

marble, in the right side of the neck, 1 inch (2.5 cm) below the angle of the jaw and anterior to the sternocleidomastoid muscle. This grew slowly and steadily. At times, especially in summer, it seemed to be smaller, but it never disappeared. The lump seemed to enlarge with winter colds and on occasions was large enough to give a sensation of pressure under the skin. One year previously a similar lump had appeared on the right side and had grown steadily. During the past year a number of lumps, above and below those mentioned, had appeared. Eight months previously a hard, irregular mass 2 to 3 cm in diameter had appeared in the left submaxillary region and had grown rapidly until it filled the entire neck. This mass was purplish. There was no pain or tenderness. Two months previously the patient had noticed hoarseness, a change in the voice

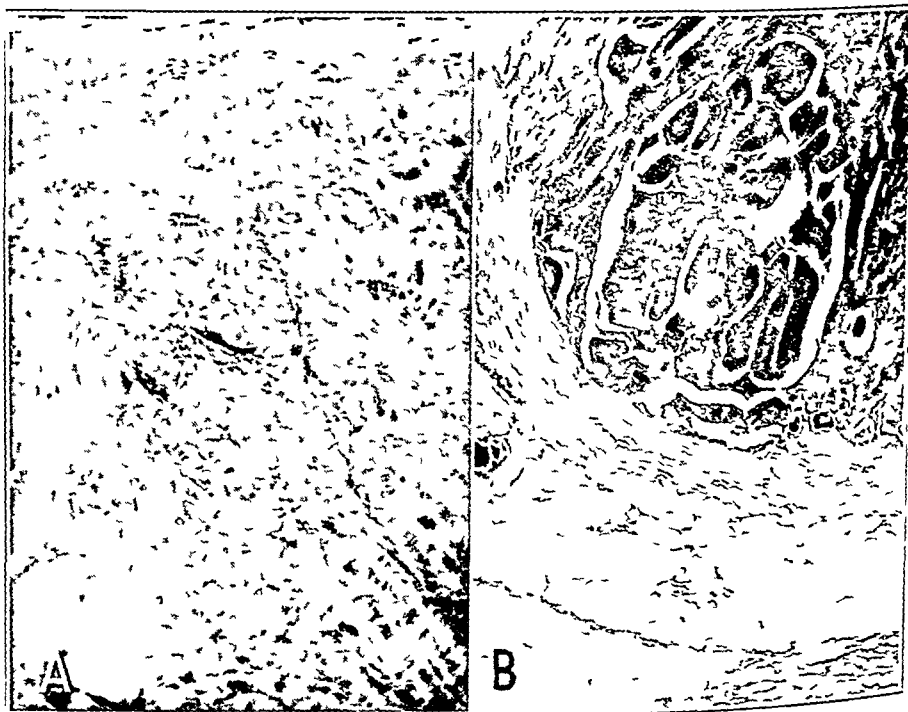


Fig 9 (case 5) —Photomicrographs of tissue removed from J. O. A, biopsy specimen showing papillary carcinoma ($\times 120$). B, tissue removed at operation after roentgen therapy ($\times 45$), showing the seminecrotic appearance of the treated tissue.

and a sense of pressure in the neck. Difficulty in swallowing, pressure in the shoulder and occasional occipital headache had been present for the past month. In January 1932 his local physician had attempted aspiration and obtained only blood. A and B, figure 8, show the appearance of the masses when the patient was first seen by me. In these photographs one can see a separate nodule under the right jaw, and others were palpable in both lateral triangles of the neck.

A biopsy done on March 27 showed papillary carcinoma in a lymph node (fig 9 A).

Roentgen treatments were given from March 29 to April 12. A dose of 1,225 roentgen units was given to each field, anterior and posterior, 800 roentgen units at one sitting being equal to 1 skin erythema dose. The patient entered the hospital

again on June 7, at which time a slough had occurred (fig 8 C and D) On June 9 the anterior half of the sloughing mass was removed surgically, and on June 15 the neck was dissected, most of the remaining malignant tissue being removed At this operation 18 millicuries of radium in seeds was inserted in the irremovable portions of the tumor At the time of operation tumor tissue was found invading the apex of the left pleural cavity, and the pleura was torn, permitting entrance of a small amount of air

Pathologic examination revealed papillary carcinoma, showing the necrosing effect of roentgen therapy (fig 9 B)

The patient left the hospital in three weeks and returned to his home, where he died on August 8 Autopsy revealed empyema of the left side of the chest as the cause of death No recognizable cancer was observed at autopsy in tissues from the neck Necrotic tissue was present, extending from the neck into the mediastinum

Comment—There seems to be little question that this process was originally extrinsic to the thyroid gland It is also likely that a similar growth appeared shortly in the gland itself and that both were of a low grade of malignancy from the onset The tumor was apparently markedly sensitive to radiation (figs 8 and 9) Although no tumor tissue was observed at autopsy, which was performed at the county hospital, it is hardly conceivable that there were no viable tumor cells in the necrotic tissue extending from the hyoid bone to the mediastinum and that the patient would not have suffered later from a recurrence

Since treating this patient I have been loath to attempt extensive preoperative roentgen irradiation because of the danger of sloughing of the skin secondary to necrosis of a large underlying tumor The patient in this case, like the one in case 3, might have survived for years after a radical removal of the tumors and postoperative irradiation had not the empyema supervened

CASE 6—J R E, a white boy 8 years and 10 months of age, entered the hospital July 15, 1931 with a complaint of difficulty in breathing while swallowing and some dysphagia for two or three years He was always warm, even when others were cold He had been nervous and irritable the past year as compared to former years Swelling of the glands on the right side of his neck had been noted by his mother for one day a year previously and had been thought to be mumps

In December 1930 an enlargement of the thyroid was noted by his grandmother This had not changed up to the time of examination, according to his mother's occasional measurements

Physical examination on admission showed that the thyroid gland was about three times the normal size It was larger on the left and, though not adherent to the skin, was apparently fixed to the deep structures At the upper left pole was a nodule the size of a pecan, attached to the body of the lobe by a slender connection The gland was firm throughout and was nodular There was no apparent substernal extension All lymph chains in the neck showed enlarged glands from pea to walnut size, firm and discrete, but in a continuous chain The sternocleidomastoid muscle bulged laterally because of underlying nodes

At this time the basal metabolism rate was +47 and +42 per cent Roentgen study of the chest showed diffuse mottling of the lung fields The patient was given roentgen therapy every three weeks from July 1931 to January 1932

On his reentry into the hospital, on June 6, physical examination showed essentially no change. At operation, on June 9, a stony hard area was found in the left lobe of the thyroid gland, which appeared to be invading the trachea. The left lobe and isthmus of the gland were resected, including a chain of aberrant nodes extending along the left neurovascular bundle. The operative diagnosis was carcinoma.

Pathologic examination showed a uniform picture (fig 10).

The patient had a stormy postoperative convalescence, the temperature rising to 39.2 C (103.1 F) on one occasion.

Roentgenograms of the chest taken September 17 showed that the lung fields were uniformly mottled from apexes to bases. These pictures when compared



Fig 10 (case 6)—Photomicrograph ($\times 120$) of tissue removed from J. R. E. This is a typical picture of the Langhans proliferating goiter and was present in all specimens from the thyroid gland and the lateral aberrant chain.

with those of 1931 and June 1932 showed that the mottling was slightly greater. The roentgenologist concluded that such a picture could be produced equally well by miliary tuberculosis or miliary carcinomatosis. In either case, the clinical development seemed to be extremely slow.

On December 27 the boy appeared to be perfectly well and free of symptoms. The basal metabolic rate was +16.5 per cent. The von Pirquet reaction was negative for human and bovine tuberculosis. The roentgen findings were essentially the same as of the last examination. The roentgenologist stated that the lack of progression in the process would seem to point to diffuse fibrosis, possibly on a tuberculous basis, although carcinoma could still not be ruled out.

Roentgen examination on April 12, 1933 showed the lesions in the lungs to be slightly larger, and on August 16 a further increase in size of the nodules, especially at the base of the right lung, was noted. On Jan 16, 1934, the basal metabolic rate was +135 per cent, and roentgen examination showed the lungs much the same as at the last examination. A calcified gland could be seen to the left of the thyroid cartilage, which suggested an old tuberculous lesion. On September 2 the basal metabolic rate was +2 per cent, and roentgen examination showed no change. The von Pirquet reactions were still negative, and the boy appeared to be in excellent health.

He remained well until June 15, 1936, when he entered the hospital with a complaint of malaise, fatigue, anorexia and night sweats of four weeks' duration. He had had a fever for two weeks. At this time his reaction to tuberculin was 4 plus in twenty-four hours for human and bovine antigens. A guinea pig test and a stain for acid-fast bacilli gave negative results. Not enough change could be seen in the thoracic film to make sure that it was different from the last examination. His symptoms subsided promptly on rest.

In March 1937 the basal metabolic rate was +63 per cent. Roentgen examination of the chest showed no essential change. Cutaneous tests for coccidioides gave negative results.

On August 23 the basal metabolic rate was +8 per cent, and roentgen examination showed the nodules in the lungs apparently no larger than the proportionate increase in size of the patient would warrant.

On July 6, 1938 the boy was healthy and apparently normal. Roentgen examination showed no change in the pulmonary condition.

At the time of his last examination, on July 31, 1939, the thoracic film was unchanged (fig 11), the basal metabolic rate was -10 per cent and nodules could be palpated along both sternocleidomastoid muscles.

Biopsy of material from a palpable node in the left side of the neck showed no tumor tissue or tuberculosis.

Comment—This case has many interesting and contradictory features. In the first place, a toxic nodular goiter giving rise to a basal metabolic rate of +50 per cent is very rare in an adult and unique, in my experience, in an 8 year old child. Roentgenograms of the chest showed a diffuse mottling one year before the operation, and this condition progressed slowly up to 1934, two years after the operation. During all this period his reactions to tuberculin remained negative. In January 1934 calcification was noted by roentgen study in the recurrent or persistent nodules in the neck, with a still negative reaction to tuberculin in September of that year. Suddenly, in June 1936, with fever and symptoms of tuberculosis, the child gave strongly positive reactions to human and bovine tuberculin, but there were no progressive changes in the lungs. If the roentgen findings were due to miliary carcinomatosis, the condition should have continued to progress, if they were due to tuberculosis they should have flared up with the acute infection. The fact that the lesions in the chest have remained dormant or progressed very slowly is still not proof against their malignant nature, as Kennedy⁴

⁴ Kennedy, R. L. J. Carcinoma of the Thyroid Gland in Children, *J. Pediat.* 7: 631-650, 1935, personal communication to the author.

reported a case in which a patient 10 years old survived seven years after the first roentgenograms showed pulmonary metastases. Through a personal communication it was learned that this patient finally died, ten years after roentgen evidence of pulmonary metastases was first shown. Except for the microscopic picture this case and Kennedy's are almost identical, even to the appearance of calcification in the cervical nodes.

The microscopic pattern of the tumors (fig 10) in this case was that of the Langhans proliferating adenoma and nowhere showed the papillary design. This type of growth, when seen in adults, is prone to spread by invasion of the blood vessels. I have considered this tumor



Fig 11 (case 6)—Films of the chest taken July 31, 1939. The diffuse mottling present has progressed only slightly since its discovery in 1931.

malignant because of the tracheal invasion found at operation, the microscopic invasion of the thyroid tissue and capsule in both thyroid and lateral tumors and, finally, what I feel to be metastases to the lungs. Despite this last finding, the degree of malignancy must be low to have permitted survival for eight years and apparently continued health of the patient up to the present time.

CASE 7—I H., a white woman 43 years of age, was first seen Oct. 29, 1929. She stated that two weeks after the birth of a child on July 12, 1927, she first noticed a lump on the right side of the neck, which steadily increased to twice the original size. She felt an occasional dull pain in the mass and it was tender on pressure. She had a grating sensation in her ear when the mass was palpated. With her pregnancy she lost in weight from 200 pounds (90.7 Kg) to 170 pounds.

(771 Kg) and had remained the same since Nervousness and irritability had been present for one year and menorrhagia for the past six months

Physical examination revealed a large lobulated mass under the upper end of the right sternocleidomastoid muscle, four isolated nodules lateral to its lower end and a nodular enlargement of the right lobe of the thyroid gland The preoperative diagnosis lay between branchial cysts and adenomas of the thyroid gland with tumors of lateral aberrant thyroid tissue

At operation, Oct 30, 1929, a diagnosis of malignant tumor was made Multiple nodules were removed from the right lobe of the thyroid gland, and one large and a number of small partly cystic nodules were removed from the area of the carotid sheath On pathologic examination all showed the same picture, which was diag-



Fig 12 (case 7) —Photomicrograph ($\times 45$) of a specimen removed from I H This papillary pattern was present in all nodules

nosed as papillary adenocarcinoma with metastases to the regional lymph nodes Postoperatively the patient received roentgen therapy, 3,000 roentgen units to the neck in weekly treatments from Dec 5, 1929, to June 4, 1930 She had had no signs of recurrence up to May 29, 1939

Comment—This is apparently a typical instance of lateral aberrant thyroid tumors with a similar type of growth located in the thyroid gland I cannot agree with the pathologic diagnosis, which called the lateral tumors metastases in the neighboring lymph nodes, but think the process originated laterally and medially at about the same time, probably owing to the endocrine demands of pregnancy The micro-

scopic picture is typical of the papillary cystadenoma so frequently seen in lateral cervical deposits (fig 12) The tumor has been placed in the malignant group because areas of invasion of the blood vessels and of the capsule were seen on microscopic examination The tumor was of a very low grade of malignancy, as was shown by its almost pure papillary form and the ten year period of freedom from recurrence after excision and roentgen therapy

CASE 8—A S, a white man 21 years of age, was first seen on March 30, 1936 He stated that he had been well till one year previously, when he had noticed a soft, nontender mass lateral to the outer border of the lower end of the

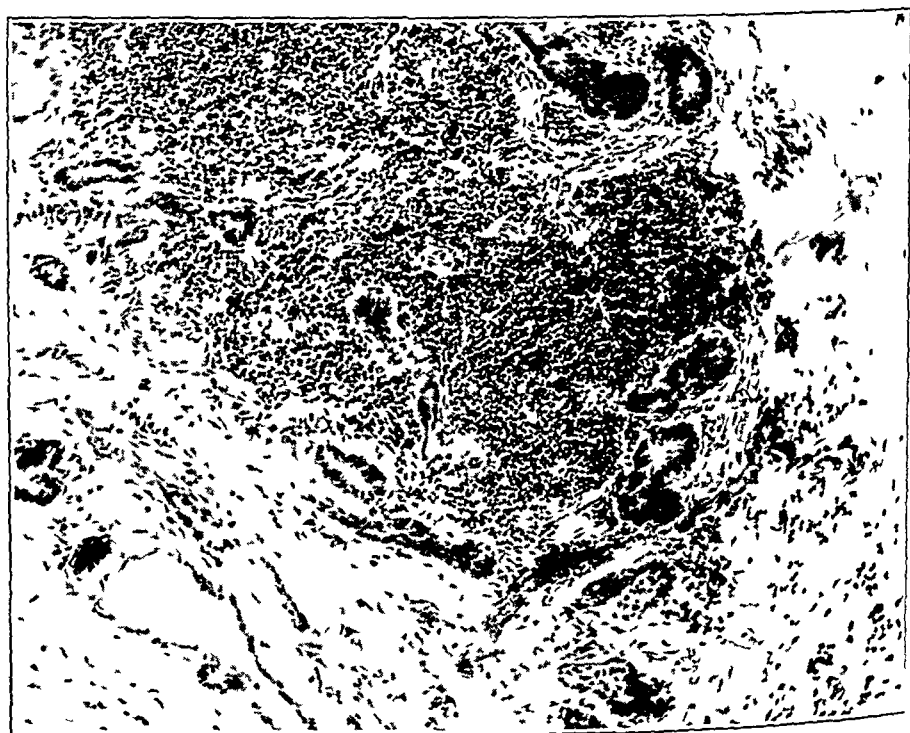


Fig 13 (case 8) —Photomicrograph ($\times 120$) of tissue removed from A S Thyroid alveoli are seen in a stroma of lymphoid tissue embedded in the wall of the cystic mass

right sternocleidomastoid muscle No symptoms were evident Two months previously the first mass had begun to grow, and a second had appeared medial to it During this time he had noticed slight discomfort in the region, but no actual pain Three weeks before consulting me he had definite pain, tenderness and stiffness extending up toward the ear after a hard day's work This disappeared the following day He had consulted his local physician a week previously

Physical examination on the day of his first visit showed a mass 4 by 4 cm, which appeared to be a thick-walled cyst, questionably fluctuant, with an extension beneath the sternocleidomastoid muscle, toward the midline There was no motion of the mass with swallowing The thyroid was not palpable

At operation, on March 31, a lateral cystic tumor with a medial extension was found lying beneath the sternocleidomastoid muscle, anterior to the carotid sheath. Nowhere was the tumor in contact with the thyroid gland, being separated from it by the ribbon muscles. It was easily removed and not adherent or infiltrating. It was considered at operation to be a benign papillary adenoma.

On pathologic examination the mass was seen to be grossly an empty sac 8 by 6 cm in diameter, covered by a smooth capsule. Microscopic examination showed epithelium extending into the cyst wall. In one area a lymph node showed a few isolated acini buried deep in the substance of the node. Difference of opinion as to the presence of malignancy was expressed by a number of pathologists who examined the specimen. The microscopic sections are shown in figure 13.

Because of the indications of malignancy, postoperative roentgen therapy (2,500 roentgen units) was given to two fields from March 31 to April 14.

The patient had remained well without signs of recurrence up to April 1, 1939.

Comment—This was an aberrant thyroid tissue tumor of fairly short duration which suddenly began to increase rapidly in size. The cystic form would have led one to expect the common papillary cystadenoma pattern. Instead, one found what presumably was a cystic condition brought about by rapid secretion of material by numerous alveolar structures embedded in a loose fibrous and lymphoid stroma. There was no tendency to papilla formation. This tumor has been deemed malignant because the microscopic picture was so typical of adenocarcinoma metastatic in lymph nodes. There is, however, always a danger of error in basing a diagnosis of malignancy on microscopic criteria alone in tumors of thyroid origin.

CASE 9—J. H. M., a white man 45 years of age, entered the hospital, in the medical service, on July 5, 1921, with a complaint of dysentery and weakness. He had a past history of syphilitic infection, inadequately treated, at the age of 24. On the present examination the Wassermann reaction was 3 plus. He had lost 20 pounds (9 Kg.) during his present illness.

He had had masses in his neck for the past fifteen years. These had grown slowly up to six years previously, since when they had apparently remained stationary.

Physical examination showed three separate tumor masses, unconnected with each other. One occupied the right lobe of the thyroid and moved with swallowing. It was a firm, single mass but apparently was not adherent to surrounding tissues. The lateral masses were separate from the central mass and were located above the right clavicle, the larger being 8 by 4 cm., roughly egg shaped, soft and freely movable. There was a small nodule of the same consistency just above it.

These masses remained unchanged by three weeks of intensive antisiphilitic therapy. Gastrointestinal roentgenograms were normal.

At operation, on July 22, what appeared to be an adenoma was shelled out of the right lobe of the thyroid gland. It measured 6 cm. in diameter. Separate masses, one 6 cm. in diameter, spherical, and one 1.5 by 2 cm. in diameter, were removed from above the right clavicle. There were no signs of infiltration, there was no connection between the median and the lateral nodules.



Fig 14 (case 9)—Photomicrographs of specimens removed from J H M
A, adenocarcinoma as shown in median and lateral specimens ($\times 120$), B, invasion of the blood vessels ($\times 45$), C, invasion of the blood vessels ($\times 120$)

Although a pathologic examination was made, no diagnosis was reported.

The patient was known to be well one year later but died of gastric hemorrhage in another hospital July 8, 1924, three years after the operation. Autopsy was not performed.

Comment—Clinically this was a typical case of aberrant thyroid tumor with a similar tumor in the thyroid gland. The condition was so diagnosed in the clinical history. When the pathologic material was reviewed, no sign of papillary pattern was discovered. The nodule from the thyroid and the lateral nodules showed the same picture (fig 14 A). The remarkable feature common to all the specimens was massive invasion of many of the large blood vessels by tumor tissue (fig 14, B and C). Although apparently none of the tumors had invaded or penetrated their capsules, each showed penetration of the blood vessels and tumor thrombosis. This is common in malignant adenomas but rare in tumors of lateral aberrant origin. On the other hand, it is also rare for metastasizing malignant adenomas to show deposits in the cervical lymph nodes. One may therefore assume that the lateral tumors and the midline adenoma appeared at approximately the same time and became malignant at approximately the same time. I feel also that it is likely that the hemorrhage from which the patient died was due to metastases in the intestinal tract and not to a bleeding ulcer, which was certainly not demonstrable by the roentgen studies made at the time of operation.

CASE 10—D N., a white woman 29 years of age, was first seen Aug 10, 1936. About three years previously she had noticed, on turning her head, a lump just below the angle of the left jaw. This gave no trouble except an occasional ache in the nodule. A few months previously she had noted a similar nodule below the original one. Both had grown gradually, and the second one had ached a bit more than the first.

On physical examination three masses were palpable under the left sternocleidomastoid muscle, the upper one, at the angle of the jaw, was 3 cm in diameter, the middle one was 2 cm in diameter and the lower one, located at the lower end of the muscle, was the size of a lima bean. All were deep to the sternocleidomastoid muscle. The upper two were tender, the lower one was not. None moved on swallowing, and all seemed attached to muscle. The thyroid gland was palpable but was not considered pathologic.

The preoperative diagnosis was enlargement of the cervical glands, of questionable cause.

At operation, on August 11, two masses were removed and diagnosed as aberrant thyroid tissue. Other, smaller masses were seen lower in the neck but were not removed. Pathologic examination showed the specimen to consist of two well encapsulated nodular pieces of firm yellow tissue. Microscopically the nodules were well encapsulated and showed numerous small acini. Strands of fibrous tissue coursed through the section, but no pattern was maintained. Mitoses were rare. The pathologic diagnosis was aberrant thyroid tissue.

The patient was seen again on Sept 13, 1937, at which time it was noted that several masses seen after the first operation had grown gradually, especially the

one low under the sternocleidomastoid muscle, noted during the first operation. There were no symptoms. Physical examination revealed four nodules, three outside the thyroid gland and one in the isthmus.

Operation, on September 14, consisted of removal of all lateral masses and a partial left thyroid lobectomy, the lobe containing a number of small nodules.

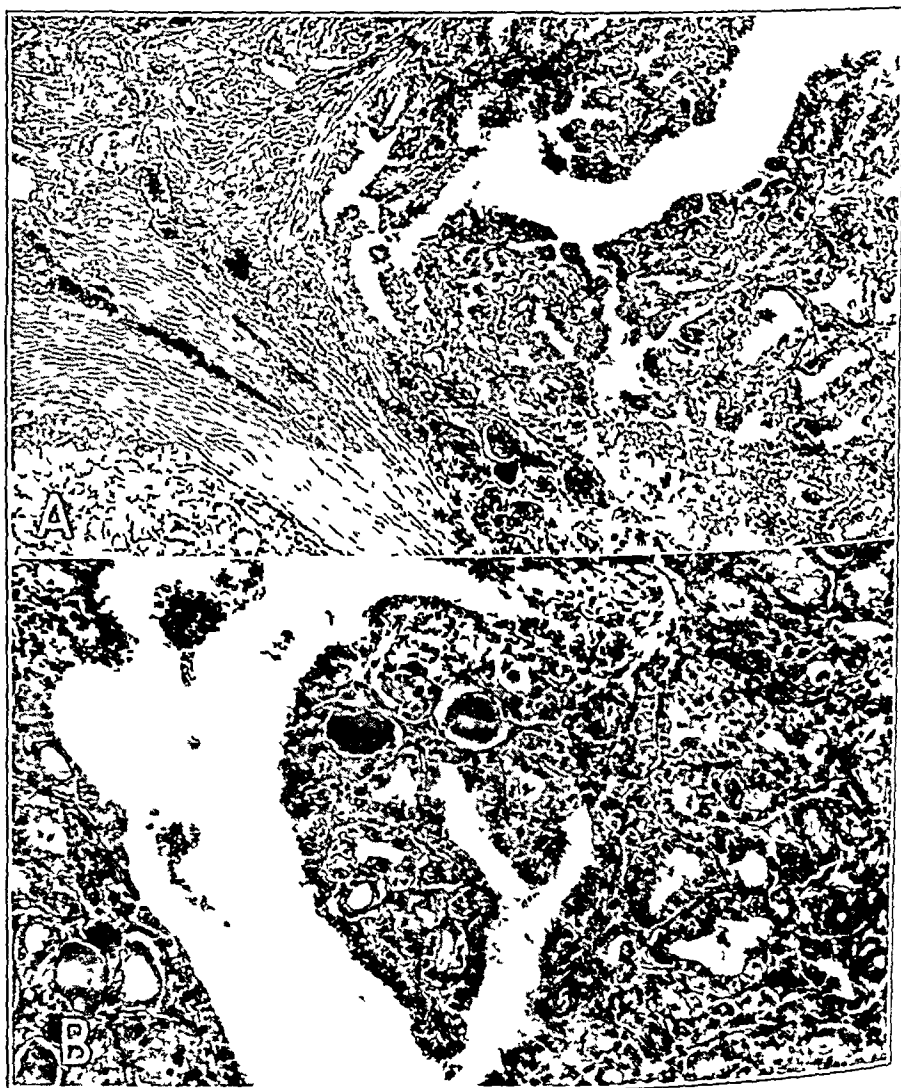


Fig 15 (case 10)—Photomicrograph of a specimen removed from D. A, area of capsular invasion by papillary tumor ($\times 45$), B, area in which alveolar pattern predominates ($\times 120$).

Pathologic examination of the specimens gave the following results. Three masses of tissue were present and were labeled A, B and C. A consisted of several masses of thyroid-like tissue, two 4.5 by 2 by 1 cm, the others 2 by 2 by 1 cm, all together weighing 25 Gm. The smaller pieces looked like lymph nodes. One of the larger pieces was encapsulated. B consisted of two small unidentified masses of fibroblastic tissue. C consisted of a rounded mass of brownish yellow

tissue, 2 cm in diameter, which was very cellular and was attached to a smaller mass 1 cm in diameter. Together the masses weighed 2 Gm.

On microscopic examination the sections showed masses of thyroid tissue, irregularly formed. Most of the cells were arranged in small acini containing little or no colloid, but many were without such an arrangement. The smallest had no lumens whatever, the cells in most areas were low columnar and had a feathery appearance. Many large lymphoid follicles were present. One such area appeared to have been a lymph node but contained a considerable amount of thyroid tissue. No vessels were seen to contain thyroid cells.

One section (fig 15 A) showed extensive invasion of a thick capsule by thyroid tissue which assumed a papillary pattern in some areas. The cells here were cuboidal and had the usual small round nucleus. However, several nucleoli were very dark. No definite mitoses were seen.

The pathologic diagnosis was aberrant adenomatous thyroid tissue, microscopically benign.

By May 1939 a new nodule was noted above the inner end of the left clavicle. The patient entered the hospital, and this nodule was removed on August 10. The mass was entirely encapsulated, showed no gross signs of infiltration and was easily removed. On pathologic examination it showed a picture similar to that of the tumors removed at previous operations. There were no indications of invasion of the blood vessels.

Comment—This was a rather typical case of lateral aberrant thyroid disease, with papillary tumors in the thyroid gland similar to those found laterally. I have placed the tumor in the malignant group because of the high proportion of the growth in which the alveolar pattern was predominant and because of the extensive capsular invasion shown in one of the nodules described (fig 15 A). Another reason for leaning toward the diagnosis of malignancy was the tendency to repeated recurrence. Again it is worthy of emphasis that microscopic criteria alone may lead one astray in the determination of malignancy and that repeated recurrence does not preclude benignancy in lateral thyroid tumors. Still, when two such factors are present a reasonable presumption of malignancy seems justifiable.

CASE 11—C. L. B. was a white girl. Her maternal grandmother, two aunts, mother and father had had goiters. She was born Dec. 30, 1932, and was seen at two to three month intervals by her pediatrician. On Jan. 21, 1936, when she was 3 years and 1 month of age, the left lobe of the thyroid was noted to be the size of a silver dollar, and a palpable chain of distinctly enlarged cervical nodes was present. From June 1936 to April 1937 there was rapid growth in all nodules. On April 2 one of the largest, on the left side, was removed.

Pathologic examination (fig 16) revealed papillary adenocarcinoma of aberrant thyroid tissue.

Many large nodules remained throughout the neck (fig 17).

From April 10 to May 13, roentgen therapy, 900 roentgen units to four 10 cm. fields, anterior, posterior and left and right lateral (with overlapping of fields), was given. She had a uniform erythema to the point of desquamation and internal reaction enough to cause soreness of the throat, dryness and pain on swallowing.

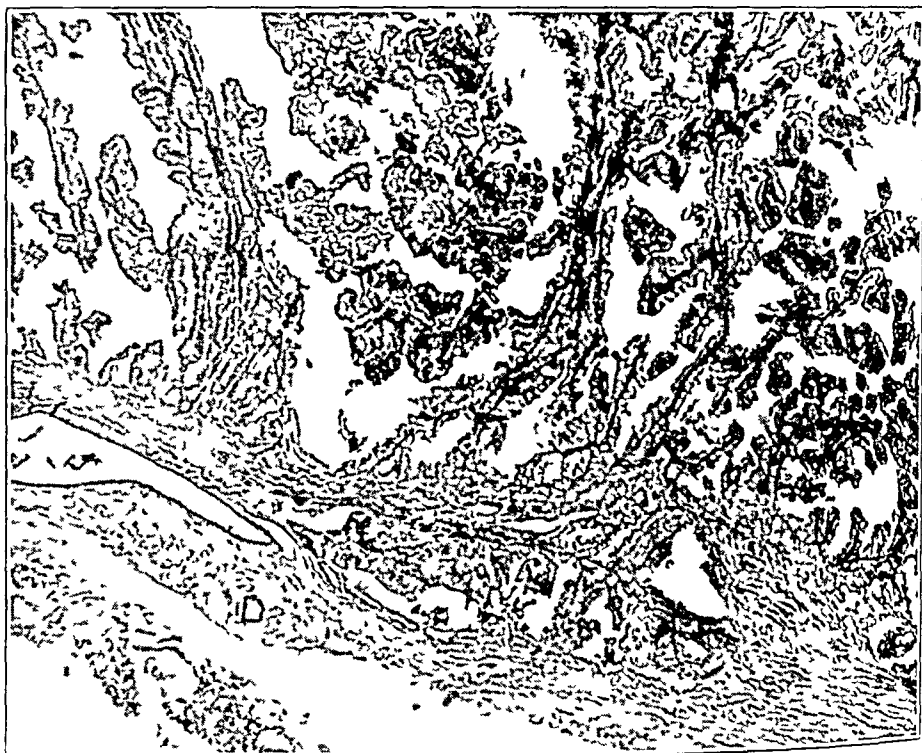


Fig 16 (case 11)—Photomicrograph ($\times 45$) of the papillary cystadenocarcinoma removed from C L B. This picture was uniform throughout the nodule removed, and was probably present in the nodules not removed.

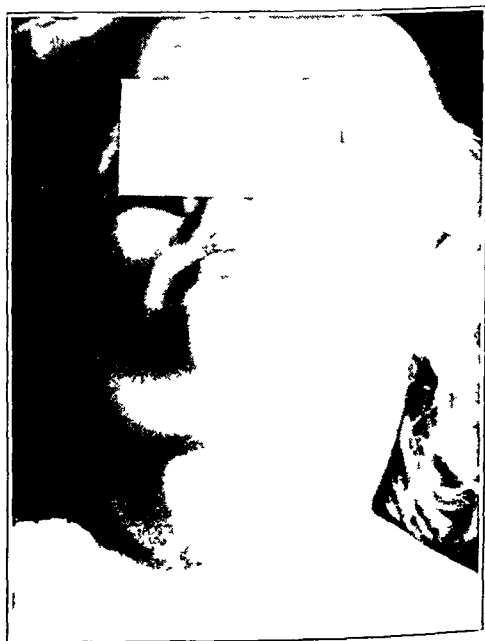


Fig 17 (case 11)—Appearance of C L B after removal of a biopsy specimen but before receiving roentgen therapy.

The child remained well, and the nodules decreased in size gradually till March 2, 1938

She was given thyroid substance, beginning December 15. She received $\frac{1}{4}$ grain (0.015 Gm) daily till November 1938, when the dose was raised to $\frac{1}{2}$ grain (0.03 Gm) daily

On June 1, 1939, two of the nodules had increased slightly in size, and the others had either decreased or remained stationary. The dose of thyroid was then increased to 1 grain (0.06 Gm) daily and is being raised gradually to a tolerance dose

Comment—This is the youngest patient I have seen with this condition. She was examined at regular intervals from birth by her pediatrician, and the first notation of disturbance of the thyroid, at the age of 3 years and 1 month, dates the onset definitely within two months of this time. The appearance of numerous nodules and their rapid progression in the following year suggest an unusual demand for thyroid secretion as the underlying stimulus. At the time operation was decided on, involvement of the neck was so general as to make an attempt at complete excision too formidable a procedure (fig 17). The material obtained by biopsy showed a uniform papillary cystadenoma type of growth (fig 16). No mitotic figures were evident, and invasion of the blood vessels could not be demonstrated, but the tumor capsule was found to be invaded almost to its outer surface by finger-like protrusions of tumor tissue showing an alveolar pattern. Because of this the process was considered malignant. Here again the criteria of malignancy were meager and were based on microscopic observations alone.

The tumors were carefully measured and diagramed before roentgen therapy was given, and there was apparent a fairly uniform decrease in the size of these over a period of months. During this time, however, some other nodules, not previously noted, appeared, and on the last examination, two years after removal of biopsy material and irradiation, there was a slight increase in size of a number of tumors. Dunhill⁵ has reported 2 cases of tumors originating in children aged 5 and 9 years which recurred repeatedly despite multiple excisions and irradiation and which disappeared on administration of fairly large amounts of thyroid substance. Although he did not deny the existence of malignancy in these tumors, he suggested that lateral aberrant thyroid tissue, because of its probably different embryonic origin, responds to the stimulus of secretory deficiency in a different way from the midline thyroid, becoming papilliferous rather than hyperplastic. The child in my case is being given increasing doses of thyroid substance at present, and the results are being closely observed.

⁵ Dunhill, T. The Surgerv of the Thyroid Gland. Tr. M. Soc. London 60: 234-282, 1937.

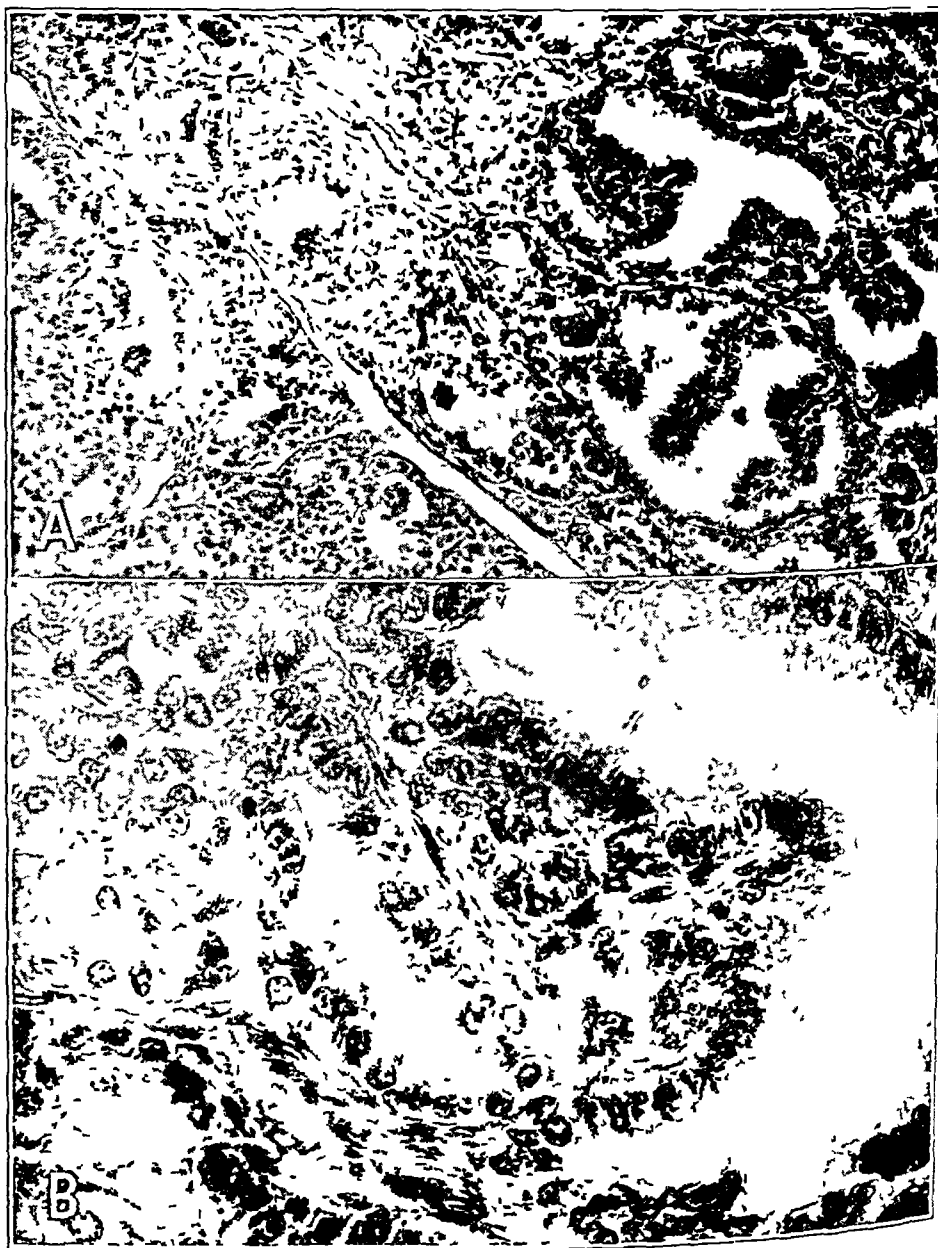


Fig 18 (case 12)—Photomicrographs of the specimen removed from C P A, one of the few areas showing the papillary design ($\times 140$), B, detail of the same area ($\times 500$)

CASE 12—C P, a white man 30 years of age, noted a small nodule in the middle of the left side of the neck two and one-half years before his first visit to the hospital Six months earlier he had observed growth in the first nodule and the appearance of other hard nodules, below the first and low in the midline

On Aug 25, 1938, physical examination showed five firm nodules from 5 to 2 cm in diameter along the course of the left sternocleidomastoid muscle They were not matted or adherent to surrounding tissue The largest lay at the level of the hyoid bone, the others extending along the sternocleidomastoid muscle to the suprasternal notch

This patient was seen one month after biopsy and again two months later The masses remaining in the neck had increased in size, and at the last examination a new mass was noted above the left clavicle Complete removal of the tumors was advised, and the patient plans to have this done at an early date

Comment—From a clinical point of view, this was a typical instance of disease of lateral aberrant thyroid tissue No tumors were palpable in the thyroid gland at the last examination The case departs from the typical in the fact that the tumor was not predominantly papillary For the most part it showed a picture of the Langhans proliferating adenoma, with large sheets of cells of uniform type, packed together In some areas a definite alveolar pattern was assumed, and the alveoli contained deep-staining colloid In only one area was a true papillary design noted (fig 18)

If I am correct in placing this tumor in the class of Langhans proliferating goiter, it can be expected to recur many times and remain benign or of a very low degree of malignancy till the patient reaches the "cancer age," at which time it may well take on the characteristics of an invasive growth and metastasize by way of the blood stream Bircher⁶ showed that such tumors are malignant in children and young adults only in that they tend to recur many times The same type of growth in patients in the fourth decade and older shows its malignancy by invading blood vessels and metastasizing widely De Quervain⁷ suggested that the repeated recurrences seen in young persons are not true recurrences but the responses of other areas to the same stimulus which caused the original neoplasm

CASE 13—M B, an Italian woman 42 years of age, entered the hospital on May 3, 1933, for biopsy of a cervical tumor With the region under local anesthesia a tumor was removed from the left superior carotid triangle, just posterior to the hyoid bone It was a spherical, bluish tumor resembling an adenoma of the thyroid, which appeared to arise from the carotid sheath and was firmly attached to the surrounding tissue The tumor was torn on removal and seemed to have a downward extension along the carotid sheath

6 Bircher, E Beitrage zur Kropffrage, die wuchernde Struma Langhans, Beitr z klin Chir **139** 383-420, 1927

7 de Quervain F Zur Kenntnis der wuchernden Struma nach Langhans in Verhandlungsbericht der zweiten internationalen Kropfkongferenz August 1933 Berne, Verlag Hans Huber, 1935, pp 650-675

The pathologic diagnosis was adenoma of the thyroid gland, of adult pattern.

On reentry into the hospital on June 12, 1933, the patient gave a history of having first noticed a painless nodule in the left side of the neck which had gradually increased to the present size without symptoms over a period of six years. The first nodule had appeared after a tonsillectomy. She had lost 10 pounds (4.1 Kg) in the past year.

Physical examination revealed no abnormality except the cervical condition, a palpable spleen and a slightly enlarged liver. There were two scars in the neck, a large one below the ear resulting from excision of a furuncle in childhood, the second from the recent removal of material for biopsy. A chain of nodules extended downward from the angle of the jaw, along the sternocleid-

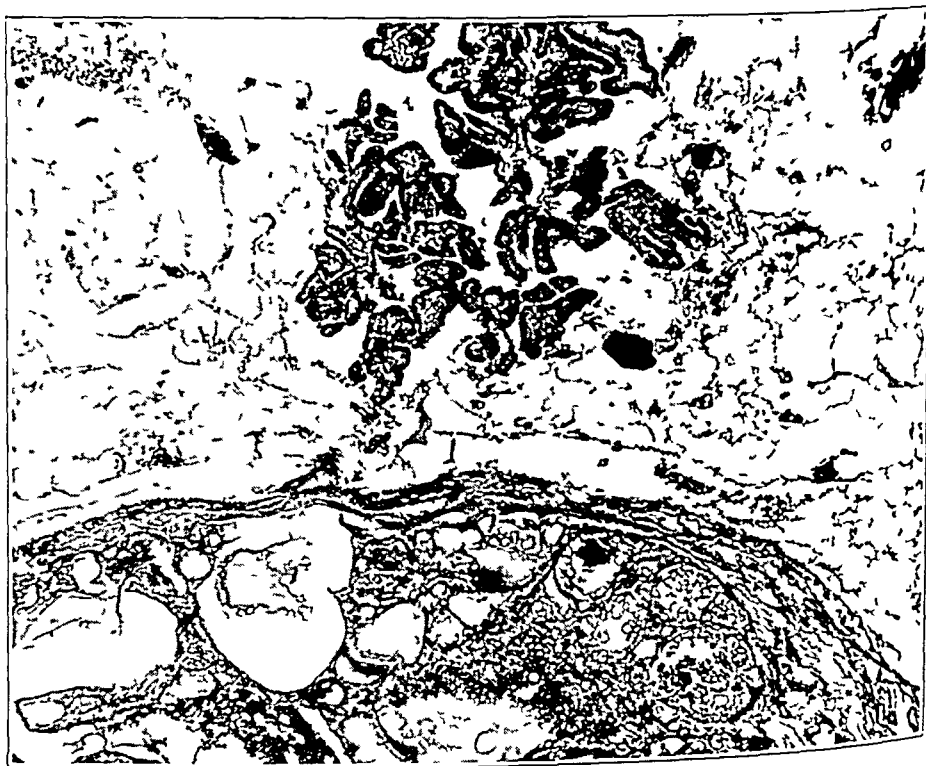


Fig 19 (case 13)—Photomicrograph ($\times 45$) of the heterogeneous picture seen in the specimens removed from M. B. Papillary areas such as that shown here were extremely infrequent.

mastoid muscle. The lowermost mass appeared to be in the upper pole of the thyroid gland.

Roentgen examination showed a series of calcified nodules in the left side of the neck and one just below the angle of the right jaw. The tumor in the thyroid was also radiopaque. The roentgen diagnosis was calcifying old tuberculous cervical adenitis and small calcifying adenoma of the thyroid gland.

The preoperative clinical diagnosis was nontoxic adenoma of the thyroid gland with lateral aberrant thyroid adenomas.

At operation, on June 13, a small nodule, 0.5 by 1 cm, was found in the midline, incorporated in the deep cervical fascia. Frozen section showed it to be a

fetal type of adenoma. The left lobe of the thyroid gland was found to be replaced by two multilocular cystic masses, the lower hugging the trachea posteriorly and measuring 3 by 5 cm. The upper nodule was one and one-half times the size of a normal lobe of the thyroid gland. Both were friable, vascular and filled with black fluid. The right side of the neck was normal. Three other masses were removed from behind the left sternocleidomastoid muscle, one, 3 by 3 cm, through the thyroidectomy wound and two others through a postmandibular incision. Postoperatively the left vocal cord was found to be paralyzed.

At pathologic examination the tissue was diagnosed as multiple large and small thyroid adenomas of adult pattern (fig 19).

One nodule remained, under the auricle of the left ear. This increased in size, and the patient reentered the hospital December 4, at which time this mass was removed and diagnosed by pathologic examination as aberrant thyroid tissue showing scarring, calcification and an approach to ossification. The patient had gained 11 pounds (5 Kg) since the last operation.

On Nov 21, 1934, a small nodule was noted above the left clavicle, which remained apparently unchanged till June 24, 1936. The patient was not seen after this date until Aug 30, 1939, at which time she had menopausal symptoms and a mechanical disturbance of the lower part of the back, but the mass above the left clavicle had not changed in size or appearance and was symptomless.

Comment—This apparently was a rather typical case of aberrant thyroid disease. The association of lateral masses with similar tumors in the thyroid gland is not unusual. Despite the persistence or repeated recurrences of the disease, I have placed the growth in the group of benign tumors because of the lack of indications of malignancy in the microscopic picture and because the complete encapsulation of all the tumors denied a tendency to infiltration of surrounding tissues. I feel that the existing mass above the left clavicle should be removed as a prophylactic measure, in spite of its apparent dormancy. There is still a threat of malignancy in the whole situation which could be expressed in beginning growth and infiltration of the existing mass or the appearance and growth of other masses.

CASE 14—J. W. C., a 68 year old white man, first consulted me on Aug 6, 1933. He had a goiter of at least twenty years' duration, which had gradually enlarged to its present size without symptoms. His father had had a goiter for many years when he died at the age of 88 from an accident. His mother had died after an operation on the breast, presumably for cancer. The remainder of his family history was not pertinent.

At operation, on Aug 7, 1933, a large, solid, fairly soft tumor was removed from the left lobe of the thyroid. There was a calcified posterior shell to this tumor. The pathologic diagnosis made was beginning degeneration in large and small adenomas of fetal type. For the most part the picture (fig 20A) showed a rather compact cellular design, such as is commonly seen in fetal thyroid glands, with a few alveoli which did not contain stainable colloid.

The patient was seen again July 23, complaining of a mass in the left side of the neck. This nodule, under the lobe of the left ear, had appeared recently. It was a freely mobile tumor mass 3 cm in diameter. After administration of compound solution of iodine for a few weeks it seemed to decrease to about half its former size. When iodine was discontinued it again enlarged.

By May 1935 operative removal was advised because the tumor had continued to grow. At this time physical examination gave negative results except for a firm, smooth, spherical, freely movable mass lateral to the left sternocleidomastoid muscle, just below the angle of the jaw. The preoperative diagnosis was lateral aberrant thyroid, and on May 3 the growth was removed. At this operation a semicystic mass 5 cm in diameter was excised through an incision which split the fibers of the sternocleidomastoid muscle near its midportion. The capsule of the tumor was torn during removal, and polypoid tissue was expressed. The

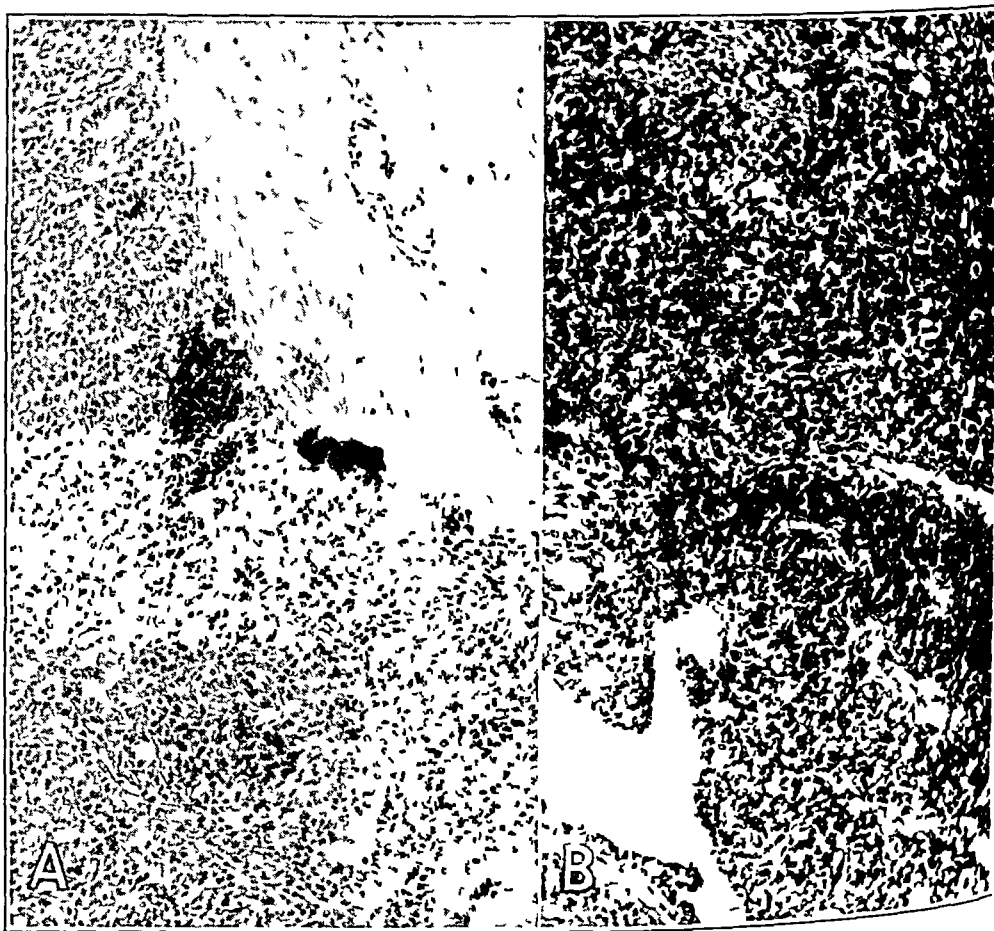


Fig 20 (case 14) —Photomicrographs of specimens removed from J W C. A, section of the original tumor of the thyroid gland ($\times 120$), B, section from a lateral nodule removed two years later ($\times 120$). Note the similarity in pattern and the absence of the papillary design.

pedicle was apparently attached to the prevertebral fascia, but there were no signs of infiltration past the capsule. The microscopic picture (fig 20 B) was similar to that of the original tumor of the thyroid removed two years earlier.

Follow-ups of this patient revealed no ill health and no recurrence of tumor, of which the patient was aware. However, in connection with this study he was examined on July 27, 1939, and a small, bosselated mass was found totaling in bulk the size of a lima bean, hard and attached deeply under the left stern-

cleidomastoid muscle at the site of the former aberrant thyroid tumor. The patient was unaware of its existence. The thyroid area showed no signs of recurrent tumor. Whether this represents scar tissue or a new nodule of tumor which will continue to grow cannot now be ascertained. There is no note of its having been present on previous examination.

Comment—This is an instance of the development of a lateral aberrant thyroid tumor one year after removal of a large, benign, non-papillary nodular goiter. Its development would suggest a response of a laterally placed embryonic rest to the physiologic demand for thyroid secretion. The apparent decrease in size of the tumor on administration of iodine is interesting, as no such effect is to be anticipated with either papillary or fetal adenomas of the thyroid gland proper. The tumor was placed in the benign group because of the lack of microscopic or gross evidence of malignancy, but the appearance of the recent nodule again raises the question of malignancy.

CASE 15—R. B., a white woman 35 years of age, was first seen on May 11, 1929. She complained of a small single lump in the left side of the neck, noted eight months previously. On examination this was found to be a single spherical nodule 2.5 cm. in diameter, apparently not attached to or infiltrating surrounding tissue. Observation was advised.

The patient was seen again on March 29, 1934. The mass had increased to 7.5 by 3 cm. in size and was palpable under the anterior border of the sternocleidomastoid muscle, at the level of the hyoid bone. The mass was freely movable upward but less so downward. The thyroid gland appeared normal.

Operation was performed on June 17, 1934, with the region under local anesthesia. A single semicystic mass lying on the carotid sheath was removed, together with a neighboring lymph node. The mass was completely encapsulated, with no signs of infiltration.

The pathologic diagnosis was benign papillary adenoma of aberrant thyroid tissue. The lymph node showed no tumor tissue.

The patient was seen in June 1939 and was entirely well, without evidence of recurrence.

Comment—This was a typical instance of papillary cystadenoma of lateral aberrant thyroid tissue except for the fact that the tumor was solitary instead of multiple. If the picture had been exclusively that of figure 21 A, the condition might be thought to have been caused by metastatic deposits of papillary adenocarcinoma in a cervical lymph node. The gross findings and the microscopic pattern shown in figure 21 B, however, lead one to the diagnosis of benign tumor. The fact that for five years the patient has been free from recurrence or the appearance of other tumors lends weight to the diagnosis of a benign condition.

CRITERIA OF MALIGNANCY

The most difficult problem in connection with tumors of lateral aberrant thyroid tissue is the determination of malignancy. This is true also of thyroid tumors in general, and the same criteria have been



Fig 21 (case 15)—Photomicrographs of specimen removed from R B ($\times 120$) *A*, section from the capsule of the nodule in which tumor cells can be seen in alveolar formation and in patternless sheets embedded in a lymphoid stroma, *B*, papillary pattern typical of that part of the tumor which protruded into the lumen of the cyst

applied to both classes of tumors⁸. In the papillary tumors there is little to indicate that one is malignant and another benign. Moritz and Bayless,⁹ determined malignancy by the presence of invasive qualities in the growth. If microscopic evidence of invasion of the capsule, blood vessels or lymph nodes was present, the tumor was considered malignant. Regional or distant metastases were considered gross evidence of malignancy. I have also used these findings as diagnostic signs of malignancy. It must be emphasized, however, that multiple lateral tumors, whether accompanied by similar tumors in the thyroid gland or not, do not constitute evidence of malignancy per se and that the presence of lymphoid elements in lateral tumors does not necessarily indicate that they are metastases to lymph nodes.

POSSIBLE CAUSE OF THE DEVELOPMENT OF LATERAL TUMORS

Speculation on the cause of malignant tumors in general leads to the conclusion that the malignant cell is a bad brother of the benign cell of the same organ in which the tumor arises. The malignant cell has gone out of control, and, after it has been so for a few generations, it acquires certain characteristics which help to distinguish it. These characteristics become known to the pathologist and help him to discriminate between the malignant and the benign cells in tumors of every organ and part of the body. In neoplasms of the thyroid gland this differentiation of malignant and benign cells is particularly difficult—so difficult, in fact, that most observers require more than microscopic evidence of malignancy before classifying thyroid tumors as malignant. It has been said by Wegelin,¹⁰ Graham¹¹ and others that a distinction between non-malignancy and malignancy cannot be made from the character of the cells, the mitoses, the structure of the alveoli or the complete absence of acinar formation. Many of the changes which would bespeak malignancy in other organs are seen in the thyroid as a response to stimulation of the gland to greater activity. Broders¹² emphasized this by calling

8 Ward, R. Prognosis of Malignant Goiter in Relation to the Pathologic Types, *West J Surg* **47** 437-448, 1939.

9 Moritz, A. R., and Bayless, F. Papilliferous Tumors of the Thyroid Gland and of Aberrant Thyroid Tissue, *Am J Path* **7** 675-689, 1931, Lateral Cervical Tumors of Aberrant Thyroid Tissue, *Arch Surg* **24** 1028-1043 (June) 1932.

10 Wegelin, C. Malignant Disease of the Thyroid Gland and Its Relationship to Goiter in Man and Animals, *Cancer Rev* **3** 297-313, 1928.

11 Graham, A. Malignant Epithelial Tumors of the Thyroid, *Surg, Gynec & Obst* **39** 781-790, 1924, Malignant Tumors of the Thyroid Epithelial Types, *Ann Surg* **82** 30-41, 1925.

12 Broders, A. C. Regenerative Hyperplasia in Exophthalmic Goiter. A Condition Simulating Carcinoma, *Virginia M Monthly* **56** 453-456, 1929.

attention to a number of cases in which regenerative hyperplasia showed such a great resemblance to carcinoma that a distinction between the two on purely microscopic grounds was almost impossible. The response to stimulation is shown in the thyroid gland by hyperplasia, formation of new alveoli lined by active cells and containing little visible colloid, piling up of epithelium of the acini and, in extreme cases, formation of definite papilliferous outgrowths into the acinar lumen. The dividing line between benign and malignant tumors of papillary structure is not sharp, and there is little evidence to show that this change from benignancy to malignancy is not a reversible process. Marine and Lenhart¹³ pointed out that goiters which develop in brook trout as a result of overcrowding will infiltrate muscles, bones and other tissues, even extending to the gills, and that these tumors regress and disappear when the conditions leading to their appearance are withdrawn. Gaylord and Marsh¹⁴ demonstrated occasional metastasis from these tumors. It is true that the thyroid gland in this fish is not encapsulated, and Marine and Lenhart¹³ concluded that this infiltrative disease is not a true malignant tumor but a hyperplastic response to stimulation which disappears when the stimulus is removed. They further noted, however, that some of the fish had true papillary tumors which did not disappear with resolution of the accompanying hyperplasia. In the first instances the process was reversible and disappeared with removal of the inciting cause, while in the latter tumors, of papillary design, there was no response to the administration of iodine, and the goiters were considered by these investigators to be true benign neoplasms. The process had reached an irreversible stage.

There is considerable difference of opinion as to the origin of lateral aberrant thyroid nodules. Weller¹⁵ recently reported studies on human embryos which suggest strongly that the lateral anlagen, which have their analogy in the ultimobranchial bodies of lower mammals, play an important part in the formation of the thyroid gland in man and that a lack of proper development and fusion with the midline anlage may be responsible for thyroid deficiency in children. d'Abreu¹⁶ gave further evidence of the lateral origin of the lobes of the thyroid gland by reporting a case of tumor of a lateral aberrant thyroid tissue in which papillary thyroid tissue was associated with a branchiogenic cyst lined by columnar ciliated

13 Marine, D., and Lenhart, C. H. Further Observations and Experiments on the So-Called Carcinoma of the Brook-Trout, *J. Exper. Med.* **13** 455-475, 1911.

14 Gaylord, H. R., and Marsh, M. C. Carcinoma of the Thyroid in Salmonid Fishes, Bulletin 32, United States Department of Commerce, Bureau of Fisheries, 1914.

15 Weller, G. L., Jr. Incomplete Embryologic Development of the Thyroid as a Factor in Infantile Myxedema, *Tr. Third Internat. Goiter Conf. & Am. Study Goiter*, 1938, pp. 110-113.

16 d'Abreu, A. L. Significance of Lateral Aberrant Thyroids, *Lancet* **2** 1476, 1935.

epithelium. It does not seem unreasonable to assume that this tissue, having a different primordial origin, might respond to physiologic stimulation in a manner different from that of the midline thyroid. If lateral aberrant thyroid tissue develops from embryonal rests, as was suggested by Wegelin,¹⁰ its response to stimulation may be the formation of papillary growths. If the factors causing stimulation are removed or altered the tumors may regress, unless they have reached an irreversible stage or unless the individual biologic factor resistant to cancer in the host is lacking. The loss of this assumed factor may explain the progression to malignancy in older persons, and the retention of it may account for the apparently benign course of many of these tumors in children. In this connection, Dunhill's report⁵ of complete disappearance of recurrent lateral tumors in 2 children on administration of large doses of thyroid substance is interesting. It would encourage one to hope that the progression toward malignancy might well be averted in one of two ways at different times of life. If supplying thyroid substance by mouth will eliminate the stimulus to hyperplasia and papilliferous change, it may be all that is required in the treatment of this condition in children. In adults, however, the danger that an irreversible change will take place or has already taken place is too great to warrant less than complete removal of all lateral tumors and the application of radiation as a post-operative measure. It may be found distinctly worth while, moreover, to consider administration of thyroid substance to all of the adult patients, especially to those showing a thyroid deficiency.

In this connection, case 90 in my series of malignant tumors of the midline is extremely interesting.

The patient was a white man, 25 years of age, who consulted me first on June 9, 1938, complaining of a recurrent goiter which was gradually constricting his trachea to such an extent that he was unable to sleep in any position without choking. His goiter had first been noticed in 1929, at the age of 16, and had been removed in March 1932. He was relieved of symptoms of pressure and was well until August 1936, the goiter then reappeared and grew until December, when a second thyroidectomy was performed. At this time the surgeon felt that he had done an almost complete removal of all remaining tumor tissue, including mediastinal and retrotracheal extensions. By May of the following year, however, the patient was aware of recurrence and felt that the goiter had grown continuously. At the time of his visit to me he presented a classic picture of myxedema. He had gained 23 pounds (10 Kg) in six months and weighed 231 pounds (104 Kg). He had a large, stony mass occupying the entire suprasternal and supraclavicular areas. The trachea was displaced to the right, and tissue could be felt to extend into the superior mediastinum. The basal metabolic rate was -32 per cent. A diagnosis of recurrent, malignant goiter with marked hypothyroidism was made, and he was given thyroid substance, 2 grains (0.12 Gm) daily for five weeks. On July 18, 1938, a total thyroidectomy was performed, and, after an uneventful convalescence, roentgen therapy was administered to the neck anteriorly and posteriorly from July 25 to August 16.

The specimen removed showed widely varied pathologic changes. Areas were present representing colloid goiter, diffuse hyperplasia and microfollicular adenoma. Finally, there was a circumscribed nodule measuring not more than 10 mm in diameter which showed a picture resembling that seen in malignant adenomas which have undergone a transformation into giant cell or polymorphic cell carcinoma. Figure 22 illustrates some of the pictures represented. In some zones there were a few mitotic figures, but not many. Invasion of blood vessels was not demonstrated. In many places deep in the capsule was observed what appeared to be nonmalignant thyroid tissue. None of these observations definitely



Fig 22—Photomicrographs of specimens removed from G S, a patient in another series. *A*, a small adenoma ($\times 5$), *B*, a field within the small adenoma resembling polymorphic cell carcinoma ($\times 75$), *C*, colloid goiter ($\times 28$), *D*, papilloma ($\times 75$), *E*, a microfollicular area ($\times 75$)

indicates malignancy, but, taken as a whole, with the history of repeated recurrence accompanied by hypothyroidism rather than hyperthyroidism, they justify placing this goiter in the malignant category. Whether the original goiter and the recurrences were brought about by a demand for increased functional activity of a handicapped gland and whether the process is reversible at the present stage remain controversial points. The patient has remained free from recurrence during the year that has elapsed since his last operation and during this time has maintained normal metabolism with from 1 to 2 grams (0.06 to 0.12 Gm.) of thyroid substance daily.

SUMMARY

Fifteen cases of tumor of lateral aberrant thyroid tissue are reported, with photomicrographs showing the pathologic changes. Twelve of these tumors I believe to be malignant, and 3, benign. Reasons are presented for placing each growth tentatively in the benign or the malignant group, but I feel that the dividing line between benign and malignant tumors of thyroid tissue is so indefinite that time and the eventual clinical result may or may not justify my judgment. As time passes, the tendency will be for more tumors to fall into the malignant class, because each patient who succumbs to the disease will necessarily be eliminated from the group of those with benign tumors, while those who die of other causes will not necessarily be added to it.

Following the lead of Dunhill,¹⁷ I believe it probable that tumors of lateral aberrant thyroid tissue may arise as a result of physiologic stimulation of misplaced embryonic rests and that elimination of the stimulus to their development may cause regression or even disappearance of the disease. The tendency toward malignant change is so great, however, that I recommend immediate removal of all recognizable tumors and recurrent growths in adults and the use of radiation after operation. Contrary to the opinion expressed by Crile,³ I feel that roentgen therapy is of definite value in controlling the growth of some of the papillary tumors in this group, if not in causing their complete regression.

Statistical comparison of malignant tumors of lateral aberrant thyroid tissue with those arising in the thyroid gland proper shows that the former are found in a younger age group, that they are more equally distributed between the sexes and that the mortality rate is less than half as great. Despite the more favorable mortality rate, however, the ratio of recurrence is high. Only 4 of the 15 patients with either malignant or benign tumor have remained free of the disease after a single operative removal. Billings and Paul¹⁸ in 1935 wrote that no deaths had been reported from papillary tumors arising in lateral aberrant thyroids. Crile³ in 1939 stated that metastases had never been proved as a cause of death. In this series, 2 deaths from papillary tumors occurred, 1 of these from pulmonary metastases, and I believe that a third death was caused by metastases from a lateral nonpapillary tumor. In view of these findings, I feel that a guarded prognosis should be given in similar cases and that more deaths will be found in the cases reported by other investigators if a sufficiently long period of observation is maintained.

Members of the staff of the University of California Hospital permitted the study and reporting of 9 of the cases in this study.

17 Dunhill (footnotes 2 and 5)

18 Billings, A. E., and Paul, J. R. Tumors of Lateral Aberrant Thyroids, Bull. Ayer Clin. Lab., Pennsylvania Hosp. 9:27-44, 1925.

PLASMOCYTOMA OF THE THYROID GLAND

REPORT OF A CASE

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In recent years increasing prominence has been given to the fairly frequent occurrence of plasma cell tumors of extramedullary origin. The commonest situation for such tumors is in the nasal and nasopharyngeal mucosa and the associated cervical structures, but their occurrence in a number of other regions, such as the lip, jaw, scalp and anus, has been recorded. In the literature there appears to be no record of a plasmacytoma arising in the thyroid gland, consequently, the rarity of such a condition justifies a record of this case. The interest of the particular plasma cell tumor to be described is not in its mere rarity, however, but in the fact that it provides a clue linking the form of thyroid enlargement known as lymphadenoid goiter, or Riedel's chronic thyroiditis, with the extramedullary plasmacytomas.

REPORT OF CASE

A childless married woman aged 50 first noticed a swelling in the neck, in the region of the thyroid gland, in January 1938. Prior to this date neither she nor her relatives had observed anything abnormal in her neck. There was no pain or other physical disturbance at the onset of her illness. The swelling slowly and steadily increased, and when she first was seen in the outpatient department of the Preston Royal Infirmary, April 1, her only complaint was of a sensation of choking when she lay in bed with her neck extended.

Examination of the neck showed a swelling conforming in outline to the shape of the thyroid gland. It was firm to hard and moved slightly on deglutition. It was free from the overlying skin, which was slightly reddened and edematous, and it was also free from the sternocleidomastoid muscles. The pulse rate was 80. There was no tremor of the hands. There was no spastic retraction of the palpebral muscles and no exophthalmos. The pupils were normal. The mentality of the patient and her general demeanor were those of a normal, unemotional person. The basal metabolic rate was within normal limits. Syphilis and tuberculosis were excluded, and roentgen examination of the skeleton showed nothing abnormal except a slightly hazy area near the head of the right humerus. Twenty-one years previously the left index finger had been amputated at the Manchester Royal Infirmary because it had become gradually swollen (without history of injury or infection) and she was informed that she might lose her arm. After this local amputation there was no further relapse in her condition, the original record of

which had been lost From the age of 36 she suffered from progressive osteoarthritis in the knees and shoulder joints, and three years prior to this examination an arthrodesis was performed on the right knee joint Before the goiter first made its appearance she had noticed that her voice failed at times, but this had not occurred recently The movements of the vocal cords were normal The only other ailment mentioned in her past history was nasal catarrh, for which she had undergone no operative treatment There was no evidence of nasal polyp

On April 5 a total thyroidectomy was performed with the patient under anesthesia induced with avertin with amylene hydrate, nitrogen monoxide and oxygen At operation it was observed that the skin was edematous on section and that there was considerable matting of the superficial structures, suggesting an inflammatory process The thyroid itself was grayish white It was uniformly enlarged and was firm to hard A section made into the isthmus confirmed these appearances and strongly suggested either a neoplasm or Riedel's thyroiditis One point in the operation was particularly noteworthy, namely, the separation of the posterior aspect of the gland from the surface of the trachea, which gave one the impression of cutting through a layer of homogeneous tissue, an impression very different from that obtained with the usual types of goiter We have noticed the same condition in sarcoma of the thyroid and in chronic thyroiditis After the operation the neck healed in the normal way, but a diffuse thickening appeared under the region of the scar and suggested extensive and rapid cellular infiltration High voltage roentgen therapy was given The swelling disappeared, and the scar became supple The neck presented a normal appearance, and this has remained up to the time of writing (July 1939) On reexamination (March 23, 1939) the pulse rate was 76 There were no signs of myxedema The patient was mentally alert but not excitable There was no abnormality in the region of the thyroid, the only disability being the chronic osteoarthritis Since the thyroidectomy a maintenance dose of thyroid substance has been given daily

Histologic Picture—The samples received for histologic study were two portions of thyroid gland, measuring respectively 20 by 40 by 70 mm and 20 by 40 by 40 mm The outer surface was nodular, with a thin intact capsule showing prominent veins The surfaces of serial slices were uniform, firm but not hard, and faint yellow They were marked by a few small hemorrhagic areas close to the capsule The appearance suggested a large lymphatic node invaded by neoplasm There was no resemblance to thyroid tissue The consistency was not that observed in the sclerotic stage of Riedel's chronic thyroiditis

Five slices were taken for histologic study, representing an area of 100 by 50 mm, after fixation in solution of formaldehyde U S P diluted 1 to 10 with saline solution, paraffin sections were stained with hemalum and eosin and with methyl green-pyronine (Unna-Pappenheim)

The greater part of all the sections was made up exclusively of plasma cells The outline of the cells was distorted by packing but retained the typical nuclear design of chromatin (figs 1 and 2) Normal lobules of thyroid gland were absent, but in most fields there were isolated acini, widely spaced among sheets of plasma cells (figs 3 and 4) The acini lacked the features of hyperplasia Where they were less packed the plasma cells showed the typical piriform, oval or circular outline with eccentric nuclei

Specific staining with methyl green-pyronine was vivid and uniform Sclerosis and prominent fibrosis were absent, but there were thin interstitial septums bounding large areas of plasma cells and invaded by them At a few points the septums

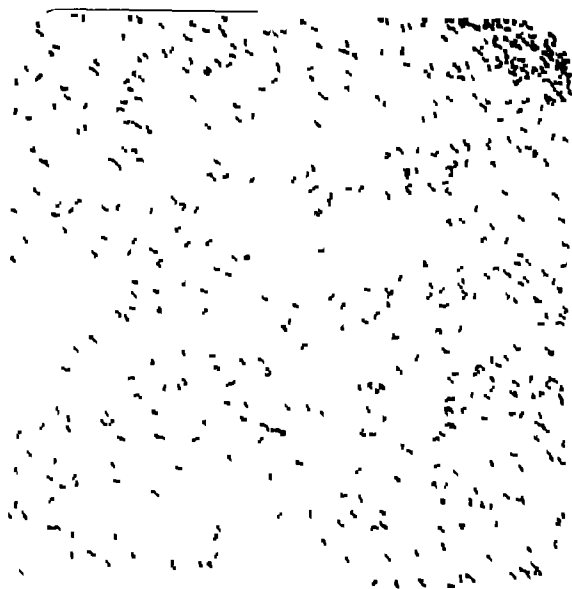


Fig 1—Dense area of plasma cells, $\times 100$

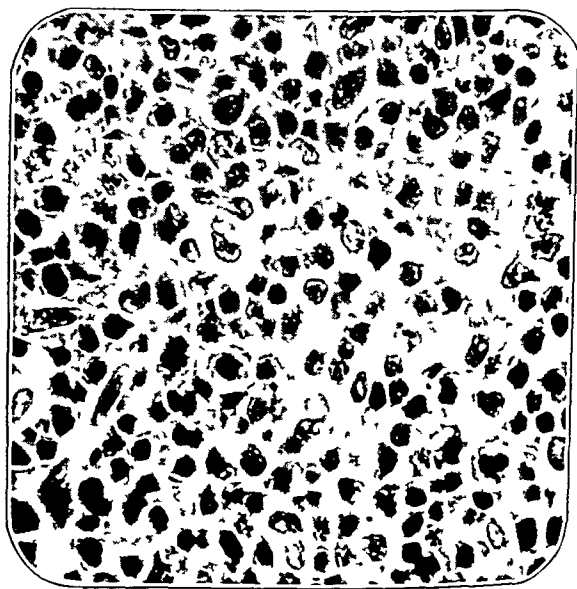


Fig 2—Part of the section shown in figure 1, $\times 550$

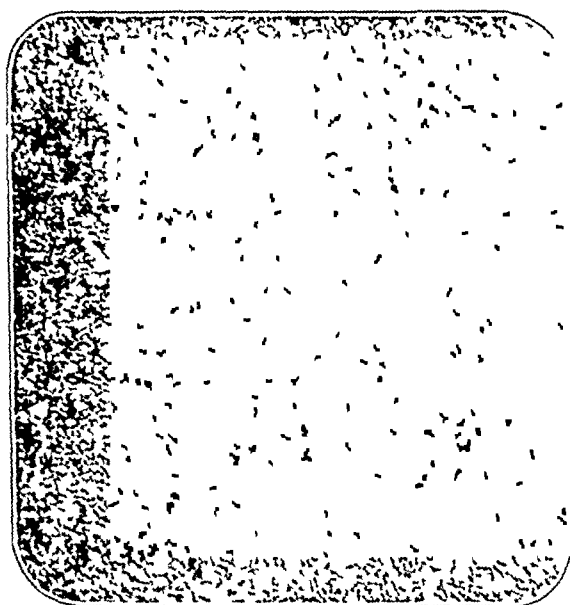


Fig 3—Isolated thyroid acinus embedded in a mass of plasma cells, $\times 100$



Fig 4—Part of the section shown in figure 3, $\times 550$

were infiltrated by small round cells. Mitotic nuclei of plasma cells were moderately plentiful, the proliferation of outlying areas suggested the low malignancy of a neoplasm rather than a reaction of inflammatory cells. Three debatable lymphoid nodes and germ centers were seen, but these were indefinite, systems of giant cells were absent.

COMMENT

The features of this case agree with an origin of the process as lymphadenoid goiter and rapid growth of plasma cells into a plasmacytoma of low malignancy, indistinguishable from the lesions of the nasopharynx reviewed by Blacklock and Macartney¹. The age of the patient is in accord with the age incidence of complete involution and atrophy of the thyroid gland as indicated by Vaux².

Two significant points emerge from the study of the clinical, macroscopic and histologic appearance of this interesting tumor: first, the dominance of the plasma cell and the relative paucity of lymphadenoid tissue, second, the resemblance of the macroscopic appearance and clinical history to those observed in cases of Riedel's chronic thyroiditis.

The preponderance of plasma cells justifies the use of the term plasmacytoma for the whole swelling, since microscopically the growth was an almost perfect example of a plasma cell tumor. On the other hand, there were definite considerations which led us to link the condition with Riedel's chronic thyroiditis.

In 1925, Shaw and Smith,³ of Newcastle upon Tyne, England reviewed the literature dealing with this condition and reported in detail 6 further cases. In all their own cases the patients were women between the ages of 32 and 58, the sex and age may thus be compared with those in the case under consideration. In cases in which operation was performed the glands were found to be firm and diffusely enlarged, they were excised with little hemorrhage. In several instances there was a considerable degree of adhesion between the gland and the trachea which caused great difficulty in the operations. In other words, the surgical findings were precisely similar to those encountered in the case under discussion. The preoperative history was also comparable, in that there was no evidence of thyrotoxicosis and no history of goiter. Also, as in our case, both syphilis and tuberculosis could be excluded.

Turning to the histopathologic picture in their cases, one finds that the cellular infiltration was composed generally of masses of lymphocytes, plasma cells and some larger phagocytic cells, the whole being lodged in a delicate reticulum of collagen fibrils and young fibroblasts, most of

1 Blacklock, J. W. S., and Macartney, C. Plasmacytoma of Nasopharynx. *J. Path. & Bact.* **35**, 69, 1932.

2 Vaux, D. M. Lymphadenoid Goitre, *J. Path. & Bact.* **46**, 441, 1938.

3 Shaw, A. F. B., and Smith, R. P. Riedel's Chronic Thyroiditis, with Report of Six Cases and a Contribution to the Pathology, *Brit. J. Surg.* **13**, 93, 1922.

the acini were altered, the epithelial cells were enlarged, the protoplasm was vesiculated, the colloid had disappeared and its place was taken by a mass of cells, many of which showed signs of degeneration, such as invasion of the cell body by phagocytes, pyknosis, crenation and chromatolysis of the nucleus. Here and there masses of cells were fused to form a giant cell. In 3 of their cases these changes were present and in the remaining 3 the lobular structure of the thyroid had disappeared and the tissue was invaded by a profuse infiltration which at first suggested a sarcomatous growth. There were lymphoid cells, plasma cells and phagocytes, and in addition there were a great number of large, pale, plump, irregularly shaped cells with fine processes, the nuclei were large and vesicular, being round, oval or lobulated, and mitoses were common. The authors considered that there were transitions between these cells and the phagocytes. Lymph follicles were absent, capillaries and other vessels were scanty, and fibrosis was negligible despite the numerous fibroblasts. The surviving glandular acini showed both hyperplastic and degenerative changes. In 1 case adipose tissue infiltrated with round cells was attached to the exterior of the capsule of the gland, and in another both muscle and adipose tissue were involved in the hyaline fibrosis that affected the capsule of the gland and involved the capsular blood vessels.

These changes may be compared with those in the case under discussion, especially those observed in the cases of thyroiditis in which there was absence of lymphadenoid tissue and fibrosis associated with hyperplasia of large plasma cells.

The progress of the disease shows that from the early stages there must be a considerable functional hyperactivity of the glandular epithelium to balance the loss of secreting tissue. It is noteworthy that even in advanced cirrhosis of the thyroid there is absence of myxedema or only very slight evidence of it, which is to be explained only by the hyperactivity of the remnants of the gland. In our case of plasmocytoma none of the early signs of myxedema could be recognized prior to operation. With regard to the cellular stroma, an interesting point has been noted by Shaw and Smith,² not only were plasma cells present in all their cases, but they were present in much larger numbers than are found in lymphoid tissue, which, the authors suggested, was evidence of an inflammatory process. Moreover, the absence of lymph follicles in 1 of their cases of thyroiditis they held to indicate that pathogenically the early stage of Riedel's thyroiditis is not a focal lymphatic hyperplasia but essentially a chronic inflammatory process. In our case there was an extreme paucity of lymphoid tissue and the field was dominated by plasma cells in all sections of the gland. It is to be noted that in Shaw and Smith's case of thyroiditis in which there was absence of lymph

follicles there were extreme destruction of the glandular acini and diffuse cellular infiltration at first resembling sarcoma, a condition of cellular change comparable to that in our case. So far it is suggested that the plasmacytoma in this case arose from a gland in which a pathologic process had occurred which might be compared with certain types of Riedel's chronic thyroiditis. The latter condition presents varying histopathologic features. The one point of distinction between this case of so-called plasmacytoma and those of thyroiditis recorded by Shaw and Smith is the exceptional prominence of the plasma cell.

Recently (May 1938) Vaux,² of the Royal Free Hospital, London, England, has reported a study of 38 cases of lymphadenoid goiter, and she found that there are three stages in the development of the lesion.

In the early stage there is scattered infiltration of the gland with proliferating lymphocytes and plasma cells and accompanying slight fibrosis. At this period the acinar cells are normal or show varying degrees of cellular hyperplasia.

The intermediate stage shows compression and distortion of the thyroid parenchyma by masses of plasma cells and lymphocytes together with the formation, both diffusely and in trabeculae, of fibrous tissue.

In the third and last stage the glandular epithelium is almost completely destroyed by fibrosis and cellular infiltration with plasma cells and lymphocytes.

This author also found that the clinical course agrees with these pathologic stages, an early stage of thyrotoxicosis being replaced later by hypothyroidism. In a similar manner, there was progressive hardening of the gland according to the stage of the disease and determined by the increasing cell pack and fibrosis. Vaux² concluded that the condition is due to excessive involution of the thyroid following mild hyperthyroidism. Tuberculous infection, syphilis and pyogenic infection were excluded. She based her view of involution on the early evidence of thyrotoxicosis correlated with the histologic observations of decreasing epithelial hyperplasia and increasing destruction of acini.

Against this view there is another aspect of chronic thyroiditis, namely, the diffuse extracapsular spread of the lesion into the muscles of the neck, involving the carotid sheath and extending downward into the mediastinum. Monod and Monod,⁴ Bohan,⁵ Ricard⁶ and Berry⁷

4 Monod, G., and Monod, R. *Étude sur la thyroïdite ligneuse chronique*, J de chir **22** 1, 1923.

5 Bohan, P. T. *Ligneous Thyroiditis Associated with High Grade Dental Infection*, M. Clin. North America **7** 1069, 1924.

6 Ricard, M. *Note sur une variété de dégénérescence fibreuse du corps thyroïde*, Bull. et mem. Soc. de chir. **27** 758, 1901.

7 Berry, J. *On a Further Series of Five Hundred Goitre Operations with Special Reference to After-Results*, Brit. J. Surg. **8** 413, 1921.

recorded cases in which the trachea, bronchi and great vessels were mantled by the cellular exudate and in a remarkable case recorded by Tailhefer⁸ the infiltration involved the carotid vessels and extended to the base of the skull. The beginnings of this extracapsular cellular spread are shown histologically in the cases recorded by Shaw and Smith,³ and macroscopically it was equally evident at operation both in their cases of thyroiditis and in our case of plasmocytoma. These changes clearly point to the operation of a cellular stimulus which in certain instances transgresses the limits of its glandular nidus and infiltrates on the same lines as the neoplasma, the process, therefore, cannot be explained as superinvolution of a normal structure. Shaw and Smith³ stated "We have been unable to collect any evidence that the condition is an involution following a previous goitre, we believe that the condition is a chronic inflammatory process of a granulomatous nature."

The recorded cases of plasma cell tumors arising in conjunction with the nasal and nasopharyngeal mucosa were reviewed in 1931 by Claiborn and Ferris.⁹ In 1 of these, recorded by Vogt¹⁰ in 1912, the tumor mass extended from the mastoid process to the jugular fossa along the sternocleidomastoid muscle. The patient died in a "choking fit." At autopsy the tumor was observed to consist of a cellular infiltration comprising lymphocytes and plasma cells. In a few areas the plasma cells were elongated and spindle shaped, resembling fibroblasts, and masses of plasma cells had permeated along the blood vessels into the musculature. In this case also the picture is one of diffuse cellular infiltration of cervical structure closely resembling advanced Riedel's chronic thyroiditis with extracapsular spread. Also, as in the case of thyroiditis, such a plasma cell tumor arising in the upper respiratory passages may develop as a well defined, distinctly localized mass of connective tissue cells forming a definite tumor or may infiltrate the surrounding structures diffusely after a primary focal development. Furthermore, the parallelism to the cases of thyroiditis and our case of plasmocytoma is emphasized by the cellular elements comprising the tumor. In addition to the masses of plasma cells there are diffusely scattered lymphocytes, however, in some cases, according to Claiborn and Ferris,⁹ lymphocytes form the predominant element. Multinucleated cells also appear, forming a still further link with our case. Lastly, it is to be noted that tuberculous and syphilitic infection were absent in all these

⁸ Tailhefer, E. Inflammation chronique primitive de la glande thyroïde, *Rev de chir* **18** 224, 1898.

⁹ Claiborn, L. N., and Ferris, H. W. Plasmocell Tumors of the Nasal and Nasopharyngeal Mucosa, *Arch Surg* **23** 477 (Sept.) 1931.

¹⁰ Vogt, E. Granulomatosis plasmacellularis colli, *Frankfurt Ztschr f Path* **10** 129, 1912.

cases of nasopharyngeal plasmocytoma, which is comparable to the findings in the recorded cases of chronic thyroiditis

The origin of the plasma cell is still debatable. One school holds that it is derived from the lymphocyte (and this is probably the more popular view), the other regards it as originating from fixed tissue, for example, the fibroblasts of the adventitia or the blood vessels. Reverting to the nasopharyngeal plasmocytomas and those occurring in other extramedullary situations, one finds that there is a division of opinion as to whether these tumors are inflammatory in origin or are true neoplasms.

Pascheff, Rados, Porkowsky, Franke and Baurmann,¹¹ describing plasmocytomas arising in connection with the conjunctivas, attributed them to inflammatory origin, and a like explanation has been advanced for plasmocytomas arising from the lip by (Kaufmann¹¹), in the anus (Albrecht¹¹) and in the jaw (Pirone¹¹). In a classification of polyps occurring in the nasal passages Alagna¹² described one type in which the plasma cell is the predominant element, and he concluded that this type of polypus is associated with infection of the nasal sinuses. Huckel¹³ cited an interesting case recorded by De Vestea, in which a massive plasma cell growth occurred in the tonsils of a man aged 82 with a strongly positive Wassermann reaction and disappeared on antisyphilitic treatment.

In the first of the 2 cases reported in detail by Claiborn and Ferris the authors could see no evidence indicating a true neoplasm. In the second case such evidence was present. Kusunoki and Frank¹⁴ considered that the plasma cell tumor in the left side of the neck observed by them was a granuloma consequent on the action of an unknown toxic agent on the walls of the blood vessels, causing transmutation of the fibroblasts of the adventitia into plasma cells.

One is thus confronted with a division of opinion as to the origin and nature of plasma cell tumors, although many of the advocates of their neoplastic nature would appear to be only half convinced. The association in our case of plasmocytoma of the thyroid gland with the changes known as chronic thyroiditis suggests that lesions occurring diffusely in the neck and lesions arising as localized masses in the nasopharyngeal mucosa (and more rarely in other places) have a common cause. In

11 Cited by Huckel, R. Ueber ein Plasmacytom des Nasenrachenraumes, Virchows Arch f path Anat 264 172, 1927

12 Alagna, G. Die Plasmazellen bei Ohren-, Nasen- und Kehlkopfkrankheiten Virchows Arch f path Anat 204 161, 1911

13 Hüchel, R. Ueber ein Plasmacytom des Nasenrachenraumes, Virchows Arch f path Anat 264 172, 1927

14 Kusunoki, M., and Frank. Ueber ein Plasmazelluläres Granulom, unter dem klinischen Bilde von Lymphomen der Halslymphdrüsen und geschwulstartigen Knoten in der Nasenschleimhaut, Virchows Arch f path Anat 212 391, 1913

all the cases mentioned, syphilis and tuberculous infection were excluded, and, although pyogenic organisms cannot be held to account for chronic thyroiditis, there is every reason for their activity in lesions of the upper respiratory passages. However, although infection in this region is extremely common, the lesions are extremely rare. The same argument is in force against their origin from a simple infection as militates against the theory of glandular involution as an explanation of thyroiditis, thyrotoxicosis is very common, thyroiditis a definite rarity. On this evidence there must obviously be other etiologic factors which initiate a stimulus resulting in so profound a change as the destruction of the thyroid gland in an otherwise healthy person or the growth of masses of tissue in the neck. Our present case affords a clue, there was evidence of long-standing osteoarticular and periarticular trophic disturbances resulting in the severe changes in the knee joints and necessitating an arthrodesis of one of these joints. The results of "sympathetic ganglionectomy" for rheumatoid arthritis and for osteoporosis have now been observed by many surgeons in different parts of the world, and these considerations lead one toward the question of a disturbance of neural control of the affected tissue and the possible role that this might play in the development of the lesions under discussion. One of us (R C S¹⁵) has shown that irritation of the sympathetic pathway to the thyroid gland between the central nervous system and the paraspinal ganglion produced proliferation and degeneration of the thyroid epithelium accompanied by cellular infiltrations of the necrotic gland tissue. This work may be compared with the somewhat similar results obtained by Cannon and also by Wilson, who used a different technic. We have also found that section of the cervical portion of the sympathetic trunk in the same portion of its pathway caused degeneration and atrophy of nerve cells in the superior cervical ganglion and hyperplasia and degeneration of cells in the thyroid acini, whereas total cervical ganglionectomy did not cause changes in the thyroid comparable to those following neural section and chronic neural irritation. These tissue changes are similar to those reported by the same writer in 1926 after experimental irritation of the nerve supply to the aortas of rabbits and confirming the results of Manouelian¹⁶ in this field. Finally, these results were partially correlated with the findings of Pearce¹⁷ and

15 Shaw, R C Nerve Irritation and Aortic Lesions, *Quart J Med* **19** 203 (Jan) 1926, Tissue Change and the Sympathetic Nervous System, Thesis, Manchester, 1933

16 Manouelian, Y Recherches sur atherone aortique, *Ann Inst Pasteur* **27**. 12, 1913

17 Pearce, R N Experimental Arteriosclerosis and Myocarditis, *Bull Johns Hopkins Hosp* **17** 94, 1906

Polettini,¹⁸ who subjected animals for six to eight weeks to repeated injections of epinephrine and produced proliferative lesions in the blood vessels which were similar to those obtained by neural irritation. Although we were not able fully to confirm Polettini's work, our knowledge of the importance of the adrenal hormone in connection with the conductivity of the neural impulse in the sympathetic system at once suggests that there is an intricate and delicate mechanism by which the passage of physical stimuli between the central nervous system and the thyroid gland or other tissue is intimately associated with the endocrine secretions, and the transference of such impulse in a normal or an abnormal manner may be dependent on a very fine physiochemical balance at the nerve endings. It is thus considered that the changes occurring in our case of plasmacytoma are one aspect (and no doubt a rare one) of the pathologic course of a condition which is itself uncommon, namely, Riedel's chronic thyroiditis, and that these conditions are expressions of tissue cell hyperplasia following a physiochemical disturbance that may be dependent on a complex cycle of causes in part due to disturbance of the neural control and in part of endocrine origin. No doubt in a few cases chronic infection may play some part in the cycle in affecting the neural apparatus, but the fact remains that these plasma cell reactions are not associated with the ordinary specific infections, and their very rarity precludes the idea that the common pyogenic organisms are a determining factor. It would seem more likely that when there is strong evidence of a definite infection in a case of plasma cell reaction the role played by this factor is comparable to that of the conditions that predispose to the development of cancer. In other words, the infection engenders cellular instability and in rare instances the conjunction of certain neuroendocrine conditions is followed by plasma cell hyperplasia. The rarity of these reactions is illustrated by the fact that in 1925 Shaw and Smith were able to collect only 25 cases of thyroiditis from the literature since 1896.

With regard to the endocrine element of these plasma reactions, it is interesting to note that all Shaw and Smith's³ patients were females and that the patients in 31 of 38 cases of thyroiditis analyzed by Vau² were also females. In this connection the findings in 1 of Shaw and Smith's cases may be recalled. In this case the adrenal gland showed changes similar to those in the thyroid. The parenchymatous tissue was left only in the central portion of the gland, and this, although much altered appeared to be cortical tissue, while the peripheral parts of the gland exhibited massive infiltration with plasma cells, lymphocytes and phagocytes. In this zone there was almost total destruction of the normal

18 Polettini, D. B. Sulle alterazioni delle pareti vascolari prodotte dall'adrenalina sia per iniezione in circolo, sia per contatto, *Arch. per le sc. med.* 43: 63, 1927.

epithelium, while there was hyaline fibrosis of the glandular capsule. There was no evidence of tuberculous infection.

In conclusion, it is advanced that the so-called plasmocytoma in this case belongs to a type of plasma cell hyperplasia which may occur in conjunction with lymphocytic hyperplasia, the two cellular elements varying in different cases. In some the plasma cell predominates, in others the lymphocyte predominates and in others the two are present in more or less equal proportions. Such hyperplasia arises as a focal lesion,¹⁹ infiltrating the surrounding tissues and forming a localized tumor. If it arises in the thyroid or in the adrenal there are coincident hyperplasia and degeneration of the normal glandular elements, which are replaced by the masses of tissue cells. The ultimate course of such a hyperplasia appears to be governed either by local tissue reaction or by cessation of the initial stimuli. In consequence the tumor mass either spreads through the confines of the glandular capsule (in the case of the thyroid) or of the fibrous wall of the pharynx, infiltrating diffusely along the muscle planes and sheaths of the blood vessels, or, on the other hand, the cellular mass undergoes fibrosis and possibly hyaline change, remaining localized to its original site.

As regards the nature of the initial stimulus, it has been shown that simple involution of the thyroid cannot be accepted as a reasonable solution for the changes occurring in thyroiditis, and yet specific and common pyogenic infections do not form the true etiologic basis. It is therefore tentatively concluded that these rare changes are due to an imbalance of the neuroendocrine control of the tissue cells in which disturbance of the neural impulse or of the physiochemical mechanism by which it is transmitted to the tissue cells results in abnormal stimuli productive of intensive proliferation of the connective tissue cells and hyperplasia and destruction of normal glandular elements. Plasmocytoma of the thyroid, chronic thyroiditis and other extramedullary plasmocytomas are all expressions of a common pathologic process.

¹⁹ Stewart, M. J., and Taylor, A. L. Solitary Plasmacytoma, *J. Path. & Bact.* 35: 541, 1932.

A NEW METHOD OF URETEROINTESTINAL ANASTOMOSIS UTILIZING PERITONEUM

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After implantation of the ureters into the colon, serious sequelae, such as hydronephrosis and pyelonephrosis, are possible. The pathologic physiology of the ureters is significant. At least six factors are interrelated.

PERITONITIS

After direct implantation the incidence of peritonitis is high. In animals this condition occurs rarely after submucous implantation. Coffey's¹ method of constructing a ureterointestinal valve aided in preventing peritonitis. Hyperperistalsis in the colon, especially after bilateral implantation, contributes to the tendency toward leakage, particularly if specialized instruments are used in the ureters or in the rectum.

INFECTION OF THE URETER AND KIDNEY

Bacterial invasion of the ureter occurs through the hiatus in the ureteral mucosa. David and Mattill² have shown that it is improbable that infection of the renal pelvis occurs through involvement of the periureteral lymphatics. Rather, extension of infection is via the lumen of the ureter. Vermooten³ has shown that ureteral elasticity is impaired by direct extension of infection from the site of transplantation. The implanted end of the ureter remains infected. Long-standing infection of the lower end of the ureter accelerates the formation of fibrous tissue, stricture, dilation and ascending infection result (figs 1 and 2). This is not true when the ureter together with its intact nerves, blood vessels and parietal peritoneum is implanted into the lumen of the sigmoid flexure of the colon. Also, reaction of the peritoneum surrounding the intramural portion of the ureter localizes and absorbs the infection.

From the Department of Surgery, Rush Medical College

Read before the Section on Urology at the Ninetieth Annual Session of the American Medical Association, St Louis, May 18, 1939

1 Coffey, R C. Physiologic Implantation of the Severed Ureter or Common Bile-Duct into the Intestine, *J A M A* 56 397 (Feb 11) 1911

2 David, V C, and Mattill, P M. Role of the Ureteral Lymphatics in Experimental Urinary Tract Infections, *Arch Surg* 2 153 (Jan) 1921

3 Vermooten, V. Transplantation of the Lower End of the Dog's Ureter. An Experimental Study, *J Urol* 32 273, 1934

IMPAIRMENT OF FUNCTION OF THE URETER

With present methods of implantation of the ureters into the rectosigmoid, trauma to the ureter is minimized only by operative care. It is well known that peristalsis is never resumed across the site of trauma. If the ureter is cut across, its innervation will not be repaired and its function will be inhibited. Hinman⁴ stated that good peristalsis constitutes the main defense against reflux and ascending infection. Trauma

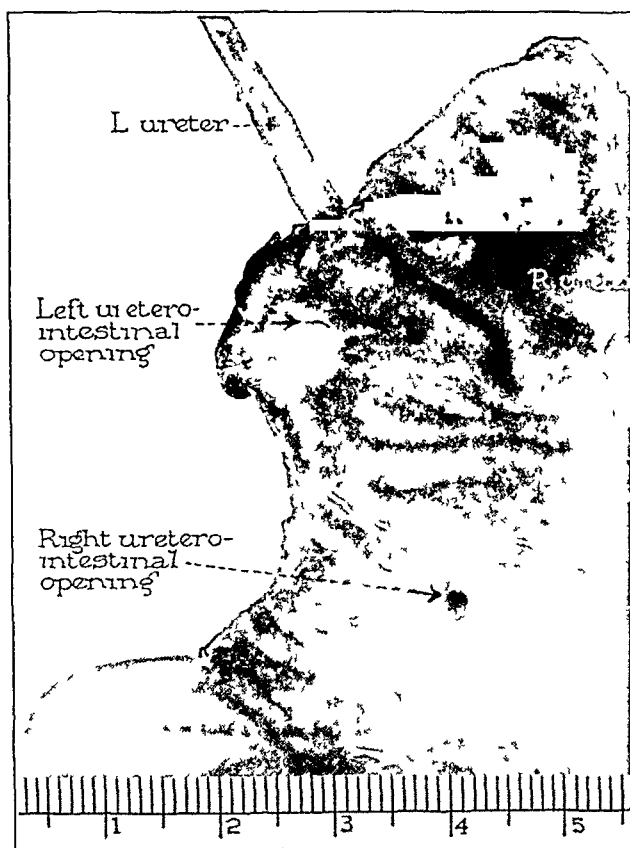


Fig 1—Specimen from typical controlled experiment. The photograph shows the uretero-intestinal orifices seven and one-half months after simultaneous bilateral implantation of the ureters into the rectosigmoid. The left ureter was dissected free from the parietal peritoneum. The right ureter was implanted with the parietal peritoneum intact. On examination the left orifice was cicatrized. The left ureter was dilated. The right orifice was satisfactory, and the right ureter was normal.

of handling and the effect of sharp dissection are important factors in the occurrence of immediate infection of the ureter, stasis in the urinary tract and subsequent renal infection.

⁴ Hinman, F. Uretero-intestinal Anastomosis, *Surgery* 2: 127, 1937.

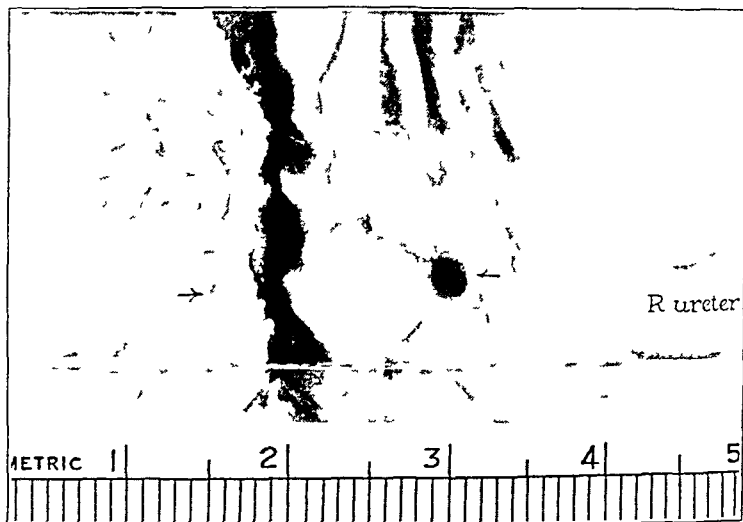


Fig 2—Specimen from an experiment similar to the one from which the specimen in figure 1 was taken, eleven months after ureterosigmoidostomy. There was a stricture of the left ureterointestinal orifice. The left ureter (not illustrated) was dilated. The right orifice was satisfactory, measuring 3 mm in diameter, and the right ureter (not illustrated) was normal.

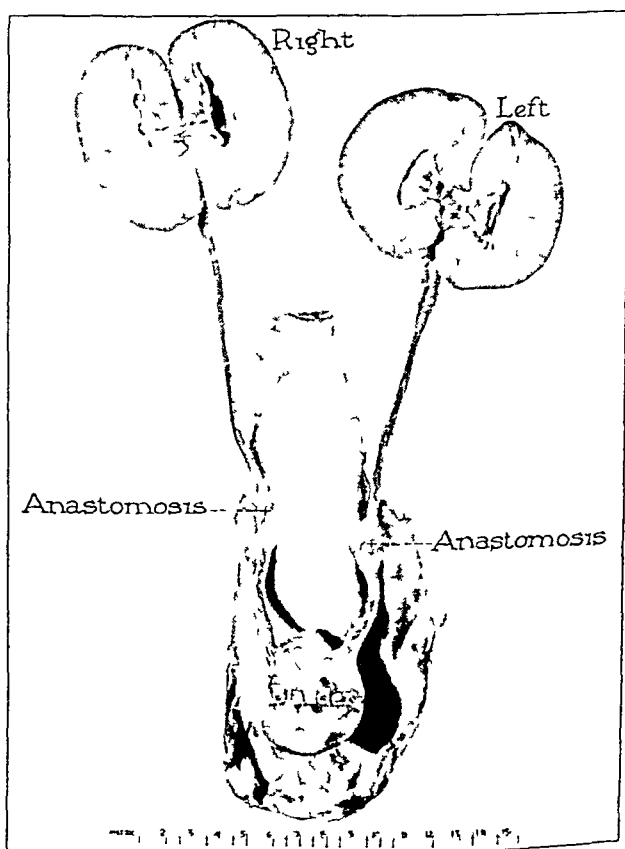


Fig 3—Specimen from a typical controlled experiment, four months after bilateral implantation of the ureters in two stages into the rectosigmoid with the parietal peritoneum intact. The proximal portion of the left ureter was anchored into the incision in the intestine by sutures in the intact parietal peritoneum. The musculature of the bowel was closed over the proximal portion of the right ureter by a suture placed over the ureter. On examination there were some hydronephrosis and pyonephritis on the right. The kidney and ureter were normal on the left.

RETRACTION OF THE URETER

Experimentally, retraction of the end of the ureter into the rectal wall is rather common. This is prevented by the Mayo⁵ modification of the Coffey method, in which the sutures of the intestinal musculature include the edge of the intramural portion of the ureter.

STRICTURE AND ANGULATION OF THE URETER

The ureter is relaxed and free of encroachment in the retroperitoneal location. After implantation into the colon its lower portion is covered for a variable distance by the musculature of the colon, and interference with peristalsis may result. If the musculature of the bowel is closed loosely over the ureter, the risk of leakage is increased, if it is closed tightly, stricture of the ureter may follow. Suture over the portion of the ureter toward the kidney constitutes a risk of stricture. Minimal encroachment on the diameter of the ureter by a scar or a suture frequently causes hydronephrosis and renal infection. By anchoring the proximal portion of the ureter into the incision in the bowel by sutures through the parietal peritoneum attached to the ureter, the possibility of stricture is minimized (figs 2 and 3). In addition, Vermooten³ found that stricture is usually present where the ureter passes through the intestinal mucosa. This possibility is avoided in a lateral anastomosis.

Since 1911, when the Coffey-Mayo¹ method of submucous implantation was reported, the older methods have been largely discarded. Walters,⁶ both alone and in collaboration with Braasch,^{6b} has contributed extensive and varied studies in the clinical application of ureterosigmoidostomy. Coffey⁷ first described the necrosing suture method, and Higgins⁸ first described the lateral anastomosis with a necrosing suture.

5 Mayo, C. H. The Formation of a Cloaca in the Treatment of Exstrophy of the Bladder, *S. Clin. North America* **1** 125, 1920.

6 (a) Walters, W. Transplantation of Ureters to Sigmoid Colon for Exstrophy of Bladder and Other Ureteral Abnormalities with Urinary Incontinence, *Minnesota Med.* **16** 416, 1933. (b) Walters, W., and Braasch, W. F. Ureteral Transplantation to Rectosigmoid for Exstrophy of the Bladder, Complete Epispadias, and Other Urethral Abnormalities with Total Urinary Incontinence. A Study of Eighty-Five Operative Cases, *Am. J. Surg.* **23** 255, 1934. Transplantation of Solitary Ureter to the Sigmoid Colon for Exstrophy of the Bladder. Report of a Case, *Proc. Staff Meet., Mayo Clin.* **9** 485, 1934. Ureterosigmoidal Transplantation for Exstrophy of the Bladder and Complete Epispadias with Absent Urinary Sphincters, *Am. J. Surg.* **24** 776, 1934. Plastic Operations on the Genito-Urinary Tract. I. Operations on the Ureters and Kidney, *Proc. Staff Meet., Mayo Clin.* **10** 529, 1935. Implantations of Ureters into the Colon, *Surgery* **2** 12, 1937.

7 Coffey, R. C. Production of Aseptic Uretero-Enterostomy by a Suture Transfixing the Ureteral Wall and the Intestinal Mucosa, *J. A. M. A.* **94** 1748 (May 31) 1930.

8 Higgins, C. C. Aseptic Ureterointestinal Anastomosis, *J. Urol.* **31** 791, 1934.

Hinman⁴ has stated that "the simplest method usually proves to be the best" All the methods of ureterointestinal anastomosis referred to⁹ (and perhaps others) are designed to minimize ascending renal infection and ureterectasis

METHOD

Intact parietal peritoneum overlying the ureter is included in a lateral submucous ureterointestinal anastomosis (figs 4 and 5) The ureterointestinal opening is established by a necrosing suture This is a mattress suture of no 6 braided silk material inserted through the parietal peritoneum and the ureteral wall on one side and the intestinal submucosa and mucosa on the other and runs parallel to the long axis of the ureter The desired length of suture should lie in the lumen

9 Bergenhem, B Ectopia Vesicae Adenoma Destruans Vesicae, Excision of the Bladder, Implantation of End of the Ureter into the Rectum, *Eira* **19** 268, 1895 Maydl, K Neue Beobachtungen von Ureterenimplantation in die Flexura romana bei Ectopia vesicae, *Wien med Wchnschr* **46** 1241-1247, 1896 Martin, F H Implantation of Ureters in Rectum A Method Having for Its Object the Making of Subsequent Infection of the Ureters and Kidneys Impossible, *I A M A* **32** 159 (Jan 28) 1899 Peters, G A Transplantation of Ureter into Rectum by an Extra Peritoneal Method for Ectrophy of Bladder, *Brit M J* **1** 1538, 1901 Fowler, G A Treatise on Surgery, Philadelphia, W B Saunders & Company, 1906, vol 2, p 313 Coffey, R C Transplantation of the Ureters into the Large Intestine, *Surg, Gynec & Obst* **47** 593, 1928 Kirwin, T J A Study of Ureteral Implantation with a Description of a New Procedure A Preliminary Report, *Am J Surg* **8** 1, 1930 Ferguson, C Experimental Transplantation of the Ureters in the Bowel by a Two Stage Operation, *Mil Surgeon* **69** 181, 1931 Beaver, M G, and Mann, F C Brief Communications Simple Method for the Transplantation of the Ureter and the Common Duct into the Intestine, *Ann Surg* **95** 621, 1932 Winsbury, H P A New Method of Implanting the Ureters into the Bowel, *Proc Roy Soc Med* **26** 1214, 1935 Hinman, F A Simple Seven Suture Method of Bilateral Uretero-Intestinal Implantation, *Surg, Gynec & Obst* **61** 802, 1935 Brenizer, A G Ureteral Transplantation Modification of Methods, *Am J Surg* **28** 210, 1935 Sherman, W L, Dinardo, C J, and Bowers, J M Ureteral Transplant Preliminary Report of a New Technique, *ibid* **29** 54, 1935 Poth, E J Aseptic Uretero-Enterostomy, *Surg, Gynec & Obst* **60** 875, 1935 Douglass, H L, and Edwards, L W Experimental Studies of Uretero-Intestinal Anastomosis, *Ann Surg* **104** 87, 1936 Hinman, F Uretero-Intestinal Implantation by Aseptic Method with Divisible Carrier Modification of Simple 7 Suture Method with Probe and Cautery, *Tr Am A Genito-Urin Surgeons* **29** 157, 1936 Altounyan, E H R Modified Coffey Operation for Transplanting Ureter, *Lancet* **2** 191, 1937 Foley, F E D Aseptic Ureterosigmoidostomy A New Method Providing Definite Asepsis in Respect to Both Fecal and Urinous Soiling a Preliminary Report, *Surgery* **2** 18, 1937 Douglass, H L, and Edwards, L W Ureteral Enterostomy Combination of Coffey, Ferguson, and Brenizer Method *J Tennessee M A* **30** 41, 1937 Farrell, J I, and Lyman, Y Aseptic Uretero-Intestinal Anastomosis, *Surg, Gynec & Obst* **66** 657, 1938 Jordan, E P Aseptic Uretero-Intestinal Anastomosis An Experimental Study, *J Missouri M A* **35** 365, 1938

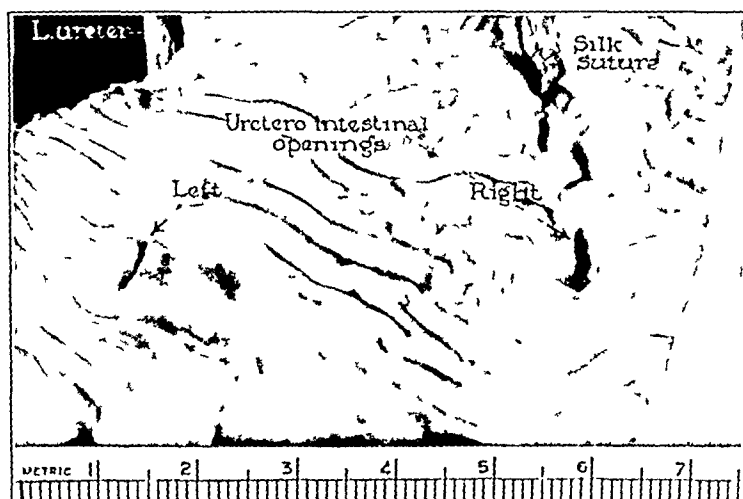


Fig 4—Uretero-intestinal orifices of the specimen in figure 3 The left orifice was 5 mm and the right 6 mm in length

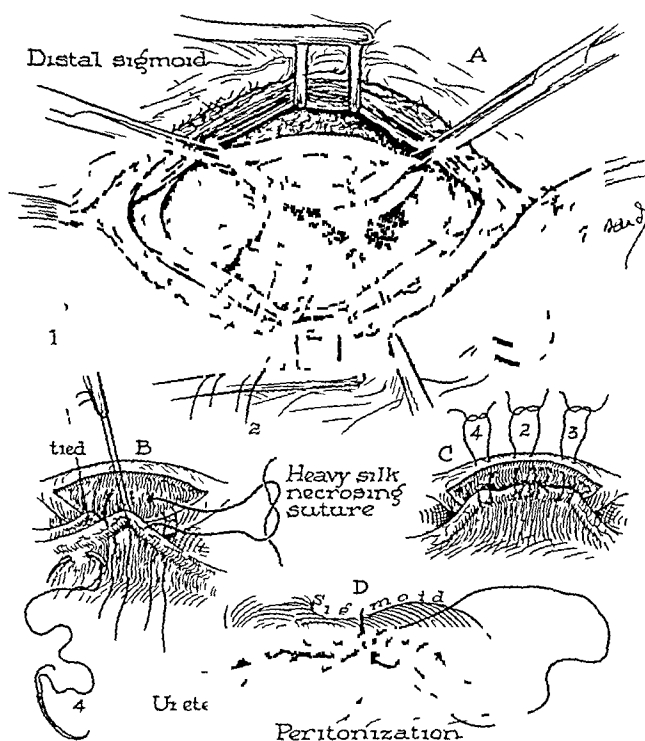


Fig 5—Various stages (A, B, C and D) in the operative technic for implantation of the ureter into the rectosigmoid The parietal peritoneum is not incised

of the ureter, this is accurately determined, and the suture is tied securely, with a crushing effect on the tissues. Care in manipulation is important to avoid breaking of the material, injury to the parietal peritoneum and contamination, especially of the abdominal wound. The longitudinal ureteral vessels are avoided. The ureter above the necrosing suture is anchored in the intestinal incision by silk mattress sutures which include, on the medial side of the ureter, the parietal peritoneum and the inferior edge of the intestinal muscle. The suture on the lateral side of the ureter includes the parietal peritoneum and the superior edge of the intestinal muscle. Sutures are not placed under the ureter proximal to the site of the necrosing suture. The intestinal musculature is closed over the ureter at the site of the necrosing suture and distally by silk mattress sutures which include both edges of the intestinal muscle and pass under the ureter. Folds of parietal peritoneum remain between the approximated edges of the intestinal wall. The field is peritonealized. The right ureterointestinal anastomosis is performed first and the left in two or three weeks.

ADVANTAGES OF METHOD

Peritoneal reaction prevents leakage and tends to localize and absorb postoperative infection. The physiologic character of the ureter is preserved by deferring ureteral section and by implantation of the ureter with the nerves, blood vessels and parietal peritoneum intact. Stricture in the proximal segment is unlikely, since the ureter is anchored in the intestinal incision by sutures in the parietal peritoneum. The probability of retraction of the ureter is minimized by adhesions between the peritoneum and the intestinal submucosa. Obstruction of the small intestine after this procedure appears unlikely.

RESULTS

Studies of animals of which intravenous urographic examination was done were made after one week and after periods up to eleven months. The roentgenologist, Dr F H Squire, studied the films and made the following reports:

Dog 1 (simultaneous bilateral transplantation of the ureters on May 9, 1938, division of the ureters distal to the anastomoses on June 13, intravenous pyelographic examination on April 7, 1939) —Both renal pelves were faintly outlined. They appeared to be within normal limits. There was some dilatation of the right ureter. The left ureter was not visualized. There was a large amount of dye in the bowel.

Dog 2 (simultaneous bilateral transplantation of the ureters on May 11, 1938, division of the ureters distal to the anastomoses on June 15, intravenous pyelographic examination on November 8) —Both renal pelves were faintly outlined appearing within normal limits. The ureters were not visualized. There was a large amount of dye in the bowel.

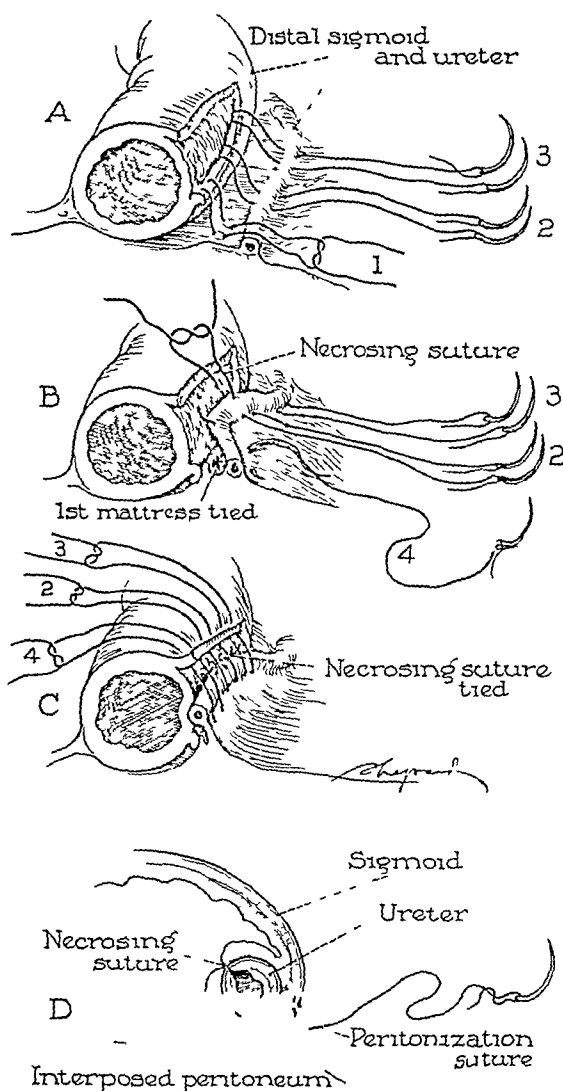


Fig 6—Sectional view of the method of operation *A*, longitudinal intestinal incision down to the submucosa, the medial peritoneal suture (1) has been placed, and the mattress sutures (2 and 3) have been passed through the inferior edge of the incision in the intestine, under the ureter at the site for the necrosing suture and distally (additional and similar sutures may be employed in that location) *B*, necrosing suture placed in the lumen of the ureter and bowel. The lateral peritoneal suture (4) is being placed *C*, necrosing suture tied. The mattress sutures (2, 3 and 4) have been passed through the superior edge of the incision in the intestine *D*, implantation completed by tying of the free ends of the mattress sutures (2, 3 and 4). The position of the ureter in the wall of the intestine, the constriction caused by the necrosing suture, the parietal peritoneum covering the ureter and interposed between the approximated edges of the incision in the intestine and the peritonealization of the superior edge of the incision into the intestine are illustrated.

Dog 3 (transplantation of the right ureter on Aug 24, 1938, transplantation of the left ureter on October 5, intravenous pyelographic examination on December 10) —The renal pelves and the ureters were not visualized, but there was considerable dye in the bowel, which showed good function

Dog 4 (transplantation of the right ureter on Oct 26, 1938, transplantation of the left ureter on November 28, intravenous pyelographic examination on April 11, 1939) —The renal pelves and ureters were normal There was a large amount of dye in the bowel, which showed good function

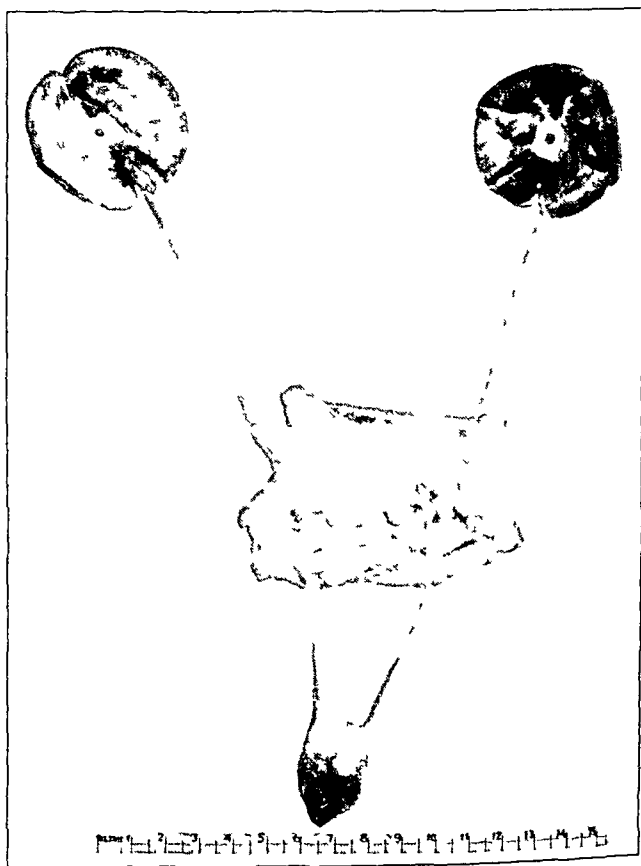


Fig 7—Specimen illustrating a typical result of implantation of the ureters into the rectosigmoid The photograph shows the kidneys, the ureters, a section of the sigmoid and the bladder six months after the operation The kidneys and ureters are normal

Dog 5 (transplantation of the right ureter on Nov 16, 1938, transplantation of the left ureter on December 11, intravenous pyelographic examination on April 4) —Both renal pelves were faintly outlined They appeared to be within normal limits There was a large amount of dye in the bowel

Dog 6 (transplantation of the right ureter on March 16, 1939, transplantation of the left ureter on April 6, intravenous pyelographic examination on April 14) —The

right ureter was within normal limits. The left kidney was well outlined and appeared normal. There was some dilatation of the left ureter. There was a large amount of dye in the bowel.

Films of specimens of the kidneys, pelves, ureters and sections of the bowel into which 16 per cent sodium iodide had been injected showed these to be within normal limits. One film of a specimen of normal ureter and kidney after injection of sodium iodide compared favorably with films of specimens treated by similar injections after operations.

The apparent dilatation seen in the pyelograms appeared to clear up after operation and was not present in the specimen. Frequently there was slight obstruction due to edema, which cleared up, as was shown in later films and in the specimens. The proximal portion of the ureter

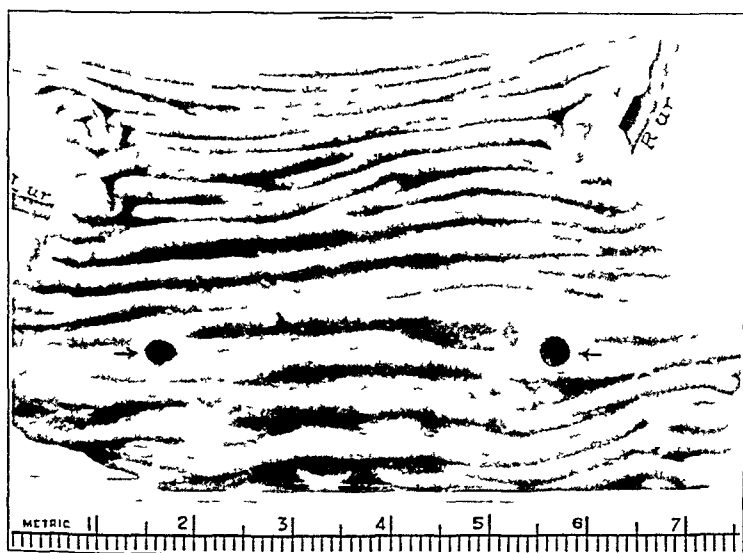


Fig 8—Ureterointestinal orifices of the specimen in figure 7. The specimen was fixed in solution of formaldehyde, with glass rods in the ureterointestinal orifices.

was not dilated, as shown in specimens removed on the third and on the fifth postoperative day.

In ten consecutive bilateral implantations in healthy dogs pathologic changes in the kidneys or in the ureters or kidneys were not observed at autopsy after periods varying from three weeks to eleven months. In 3 animals which died of extensive bronchial pneumonia within five days after the initial transplantation, bilateral pyelonephritis was observed. The transplanted ureter was not dilated in any instance (figs 6 and 7). The ultimate size of the ureterointestinal opening was 3 mm or more in diameter when 1 cm of the wall of the ureter and 1 cm of the mucosa of the intestine were included in the necrosing suture

The openings were larger than the diameters of the lumens of the ureters. The ureterointestinal orifice was devoid of excessive fibrous tissue and its edges were completely epithelized thirty-five days after

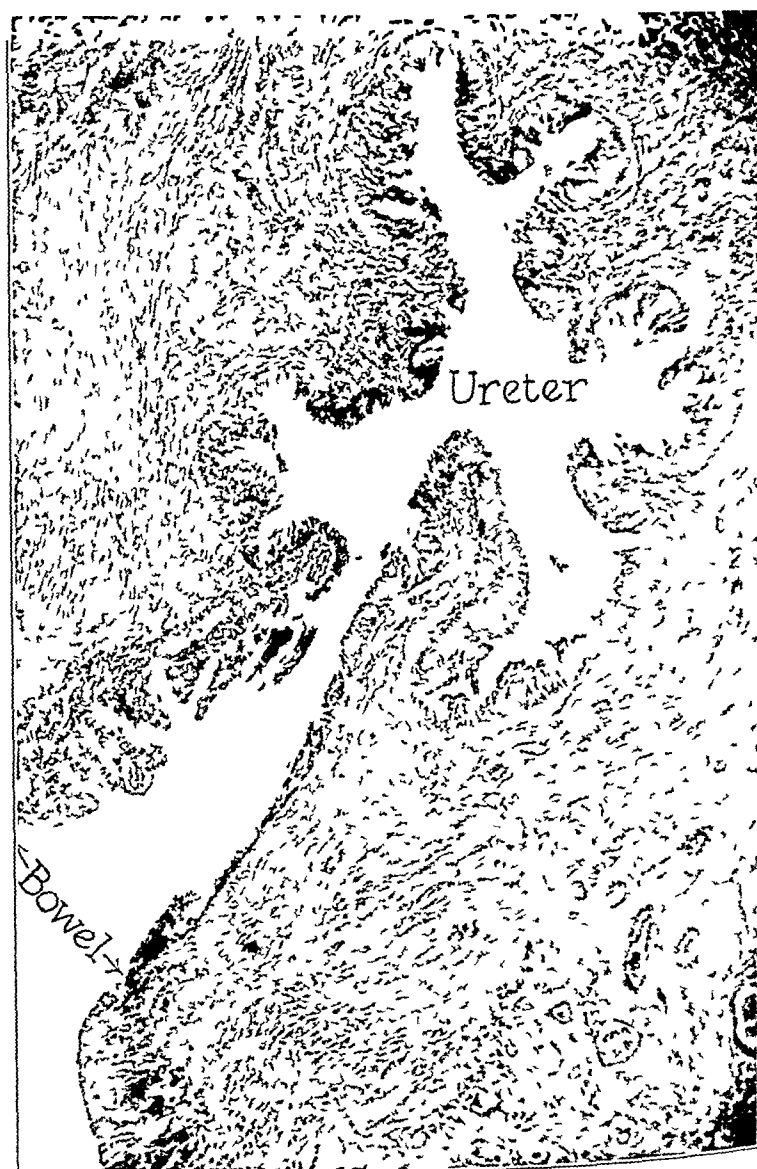


Fig 9—Photomicrograph of a section cut transversely through anastomosis of the ureter and rectosigmoid thirty-five days after ureterosigmoidostomy performed by the method described. The photomicrograph shows the anastomosis epithelized and the ureter normal.

the operation (fig 8). Urine was present in the rectum on the second day in 80 per cent and on the third day in 20 per cent of instances. The urinary stream was diverted into the intestine whether or not the ureter

distal to the anastomosis was interrupted or remained continuous with the bladder. Later section of the distal portion of the ureter in 4 instances did not alter the results.

COMMENT

The formation of a ureterointestinal fistula is soon effected because of the presence of infection in the tissue under the necrosing suture. The edema in the surrounding peritoneum increases the tension of the necrosing suture and hastens breaking down of the tissue. Growth of epithelium then completes the production of a ureterointestinal anastomosis. A necrosing suture has been employed by us in fifty-two consecutive implantations of the ureter into the colon in animals. After every transplantation the suture caused tissue necrosis which resulted in a ureterosigmoidal anastomosis. There is no tension on the ureter after this procedure, presumably in clinical application tension would be no greater than after the retroperitoneal implantation employed by Cabot¹⁰ (in 1 clinical case in which operation has been performed since the presentation of this paper, tension on the ureter has not resulted from the procedure). The chief factors contributing to the good results obtained with the method described are a ureter normal down to the ureterointestinal opening and an epithelized opening into the intestine which is characterized by the absence of scar tissue.

SUMMARY

The incidence of hydronephrosis and pyelonephrosis subsequent to implantation of the ureters into the colon has been reduced experimentally by a method which involves utilization of peritoneum and in which dissection of or trauma to the ureter does not occur.

Dr Gatewood gave counsel and guidance frequently during the eighteen months this work was in progress. Dr Vernon C. David contributed valuable suggestions and criticism in the preparation of the manuscript. Drs Willis J. Potts, Carl W. Apfelbach and Clayton J. Lundy also rendered valuable assistance.

ABSTRACT OF DISCUSSION

DR. WALTMAN WALTERS, Rochester, Minn. Dr Brackin's studies have been thoughtfully and accurately carried out and comprise one of the nicest pieces of work on experimental ureterosigmoidal transplantation which I have ever seen.

A point of great interest is that by not incising the peritoneum over the ureter one is able in creating the ureterosigmoidal anastomosis by means of the necrosing suture to prevent contracture, which Dr Brackin thinks will occasionally occur with methods in which the peritoneum is incised, and flagellation of the end of the ureter, the blood supply and nerve supply of which have been interfered with as

¹⁰ Cabot, H. The Methods of Diverting Urine Above the Level of the Bladder, with Particular References to Problem of Technic, *J Urol* 35: 596, 1936.

a result of its being removed from its periureteral tissue, particularly the peritoneum I think Dr Brackin has shown that well, because in his controlled experiments in which the ureter was pulled up from the peritoneum and the peritoneum retracted to the side, pyelonephritis occasionally occurred as a result of contracture at the necrosing anastomosis

The point relative to the importance of not placing sutures proximal to the anastomosis because of interference with motility in the ureter is important Dr Brackin has used the necrosing suture method in 52 instances in animals Also he has recently employed it in a clinical case I am sure he would want that emphasized, for the reason that there is a good deal of difference between the results of different types of ureterosigmoidal transplantation in dogs and in human beings The musculature of the dog's large intestine is much larger and thicker than that of the human large intestine

[NOTE—The patient in the clinical case referred to by Dr Walters is a boy aged 3 years with exstrophy of the bladder Sufficient time has not elapsed for urologic studies (procedure carried out May 13, 1939) However, recovery followed, and urine appeared in the rectum thirty-six hours after the operation—R E B]

A year ago, when Dr Bowman, Dr Barker and I were trying to produce atrophic unilateral pyelonephritis to note its effect on hypertension, we implanted the ureter into the bowel, using the submucosal method (the original method of Coffey), and almost without exception the subjects had first hydronephrosis and then atrophic pyelonephritis

The only way that my associates and I have been able successfully to transplant a ureter into the bowel and maintain reasonably normal function of the kidney without too much infection is to put a hole in the bowel, place a ureter in it and with a small, loosely tied purse string suture approximate very lightly the bowel around the ureter Mann found this experimentally to be the most effective method of transplanting such small ducts as pancreatic ducts in animals

One must remember that the submucosal transplantation of the ureter, the so-called original Coffey method, is followed in the dog by pyelonephritis and hydronephrosis, although these conditions may occur relatively infrequently in man, there is no doubt that they do occur

Dr Brackin's studies are particularly interesting because within fifty hours after the necrosing suture was placed urine appeared in the rectum, and urine was not present in the bladder [NOTE—Urine was observed in the bladder in various amounts after a bilateral ureterosigmoidoscopic procedure however, a greater percentage of urine flowed into the rectum—R E B] From such studies in ureterosigmoidal transplantation, which have been many and excellent, physicians are gaining a better knowledge of the fundamental physiology and pathology of the urinary tract after ureterosigmoidal transplantation

I wish to say a word of caution about the use of any method in man which may be followed by disturbing results If I remember correctly, the longest duration of any of Dr Brackin's experiments was eleven months, and in one of these prolonged experiments there was a little contracture

DR ROY E BRACKIN, Kenilworth, Ill Yes, that was a controlled experiment, and the contracture was present on the left side, where in performing ureterosigmoidostomy the ureter was dissected out and the peritoneum removed

DR WALTERMAN WALTERS, Rochester, Minn But when the peritoneum was taken off, the anastomoses persisted eleven months without contracture

DR ROY E BRACKIN, Kenilworth, Ill Yes, anastomoses were at least 3 mm in diameter

DR WALTER WALTERS, Rochester, Minn That is an important point, because with the necrosing suture method one always speculates whether ultimately contracture may not occur at the point of anastomosis

DR ROY E BRACKIN, Kenilworth, Ill There has been some question by my chief, Dr Gatewood, about the possible technical difficulties of applying the method clinically It was found, however, by postmortem measurements that the width of the sigmoid and mesosigmoid is greater at all ages than the space between the ureters at the site of transplantation

METASTASIS OF CARCINOMA TO THE SCALP

DISTINCTION FROM CYLINDROMA AND FROM CARCINOMA OF THE DERMAL APPENDAGES

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AND

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Cutaneous metastasis of carcinoma of the internal organs is of relatively infrequent occurrence. We wish to emphasize that such metastasis may be limited to the scalp and that a diagnosis even of carcinoma of the internal organs may be established first by recognition of the cutaneous metastasis and by means of cutaneous biopsy.

We wish to report 4 cases in which cutaneous metastasis of internal carcinoma was limited to the scalp, and then to discuss briefly various conditions of the scalp with which the metastatic lesions might be confused.

REPORT OF CASES

CASE 1—A white man 58 years old came to the Mayo Clinic in May 1925, for treatment of jaundice of three months' duration. He had noticed in the right upper quadrant of the abdomen a mass which had increased in size. He had lost 40 pounds (18 Kg) during the three months before he was seen at the clinic.

Physical examination established a jaundice of grade 2 on the basis of 1 to 4. The liver extended to the iliac crest, and the surface was hard and irregular to palpation. A diagnosis was entertained of carcinoma of the head of the pancreas, with metastasis to the liver.

The patient had a large lobulated tumor of the right parietal margin of the scalp, about 4 cm in diameter. There was also a small satellite nodule, which was removed for microscopic examination. The histologic picture was that of grade 3 metastatic adenocarcinoma (fig 1A). The tumor was found chiefly in the midportion and the lower portion of the cutis and was comprised of undifferentiated highly malignant tumor cells exhibiting numerous mitotic figures. Some of the cells had assumed an alveolar arrangement. No connection of the tumor cells with any dermal appendage could be demonstrated. There was relatively little inflammatory reaction.

The patient was given palliative radium therapy. He died at home in June 1926. No postmortem examination was performed.

CASE 2—A white woman 58 years old came to the Mayo Clinic in June 1931, because of weakness and exhaustion of four months' duration. The last two months

From the Section on Dermatology and Syphilology, the Mayo Clinic.

she had noticed dull pain in the left upper quadrant of the abdomen, associated with constipation, loss of appetite, nausea and vomiting. She had lost 21 pounds (9.5 Kg). Recently her stools had become hard and very dark, although blood had not been recognized.

Examination revealed a firm mass in the left upper abdominal quadrant, extending upward under the costal margin and posteriorly to the lumbar region. There were also six discrete cystlike tumors in the scalp, 5 to 10 mm in diameter, one of these tumors was ulcerating. These lesions had first appeared eighteen months prior to admission to the clinic. Two had been removed elsewhere and had been diagnosed as nonmalignant. Microscopic examination of an excised nodule revealed



• Fig 1—Metastatic adenocarcinoma of the scalp. *A* (case 1, grade 3) shows infiltrate in the midportion and the lower portion of the upper part of the cutis and a tendency toward formation of alveoli, *B* (case 2, grade 4) shows large undifferentiated tumor cells just below a hair follicle, smaller inflammatory cells at both sides and deposits of mucin in the deeper portion of the cutis.

a tumor occupying all the layers of the cutis, with some inflammatory reaction at the periphery and with a central portion characterized by deposit of mucin, revealed by special stains. A diagnosis was made of metastatic adenocarcinoma, grade 4 (fig 1 *B*).

CASE 3—A man 71 years old came to the Mayo Clinic in June 1937, because of nocturia and difficult urination of two years' duration. One week before admission he had noticed a small amount of blood in his urine.

On the morning of admission he voided large amounts of bloody urine, progressed to a condition of shock and was hospitalized. Later an intravenous urogram revealed the characteristic picture associated with tumor of the left kidney. Further examination showed multiple hard, nontender nodules in the scalp, which were less than 3 mm in diameter and which the patient thought had been present for ten days. He also had a ptosis of the left upper eyelid of two days' duration, possibly the result of metastasis to the upper portion of the nucleus of the third cranial nerve. Microscopic examination of an excised nodule of the scalp revealed the mass of the tumor in the lower part of the cutis to be composed of malignant undifferentiated cells containing numerous mitotic figures. There was no tendency toward differentiation into glandular structures. The nodule was surrounded by a dense layer of connective tissue, and the lymphatic and blood vessels were packed with malignant cells (fig 2 A).

CASE 4—A white woman 58 years old was referred to the Mayo Clinic in October 1928 by Dr M G Fronske, of Flagstaff, Ariz. In March 1928 she had first noticed small nodules in the scalp. On consulting a physician in July she had been told that she had multiple sebaceous cysts. The lesions had gradually increased in size. On Sept 27, 1928 three of the nodules had been removed and specimens sent to two different pathologic laboratories, of which one had reported the specimen to be basal cell carcinoma and the other had made a diagnosis of carcinoma arising from glandular structure.

The patient's past history was without significance. She felt well and had experienced no loss in weight or symptoms referable to any organic disorder.

Physical examination at the clinic revealed a small adenoma of the thyroid and a small cervical polyp, both of which were regarded as benign. Results of roentgenologic examinations of the thorax, stomach and colon were reported to be normal. Results of laboratory examinations, including urinalysis and studies of the blood, were essentially normal. Examination of the scalp revealed scars resulting from former excisions and two small firm nodules in the midline, one of which was ulcerated. The latter was excised for biopsy, and a diagnosis was made of metastatic adenocarcinoma, grade 3.

Some pathologists at the clinic raised the question of the possibility of carcinoma of the sweat glands, a suggestion which seemed to be supported by the essentially negative results of the general examination. We reviewed the sections of both specimens for biopsy that had been removed elsewhere, and they exhibited identical histologic changes.

Serial sections were made of the entire specimen for biopsy which we removed from the scalp. In many portions the tumor cells assumed configurations suggestive of carcinoma of the sweat glands (fig 2 B), but it was not possible to demonstrate any connection of malignant cells with sweat glands or sweat ducts. Throughout all portions of the cutis there was a dense mass of undifferentiated cells exhibiting numerous mitotic figures and showing a tendency toward an alveolar or a glandular arrangement (fig 3 A). In several regions there was approximation to and even invasion of the epidermis by the tumor cells (fig 3 B), with resultant secondary ulceration in one portion. Many of the lymph spaces were distended by carcinoma cells, although no such cells were found in the blood vessels. There was a moderate degree of inflammatory reaction, consisting of lymphocytic and polymorphonuclear leukocytic infiltration and a slight increase of connective tissue.

about the nodule of the tumor. Mucin was not revealed by special stains, a fact which tended to exclude the gastrointestinal tract as the primary focus.

Palliative roentgenotherapy was employed for the lesions on the scalp, and the patient was sent home. In January 1929 Dr Fronske informed us that she had lost 5 pounds (2.3 Kg), that new lesions had appeared on the scalp and that



Fig 2—Metastatic carcinoma of the scalp. *A* (case 3, grade 4) shows undifferentiated tumor cells filling the lymphatic and the blood vessels, which are surrounded by a dense fibrous capsule in *B* (case 4, grade 3), the arrangement of the cells suggests a carcinoma of the sweat glands.

she complained of a constant pain in her thorax. The patient died in March 1929, after development of more nodules in the scalp and an increase in the pain in the thorax. A roentgenogram of the thorax was reported to show carcinoma of the left lung. Shortly before death the patient began to suffer from severe jaundice with gastrointestinal symptoms. Postmortem examination was not performed.

METASTATIC CARCINOMA

A cutaneous metastatic lesion has no characteristic clinical appearance. Most of such tumors are nodular and circumscribed rather than of the infiltrative plaque type. The nodules are usually discrete, round or oval and are moderately firm on palpation.

Suzuki¹ found that the lesions in 98.4 per cent of his cases and also the lesions in those cases he collected from the literature were of the circumscribed, nodular type. Usually there is no attachment to the

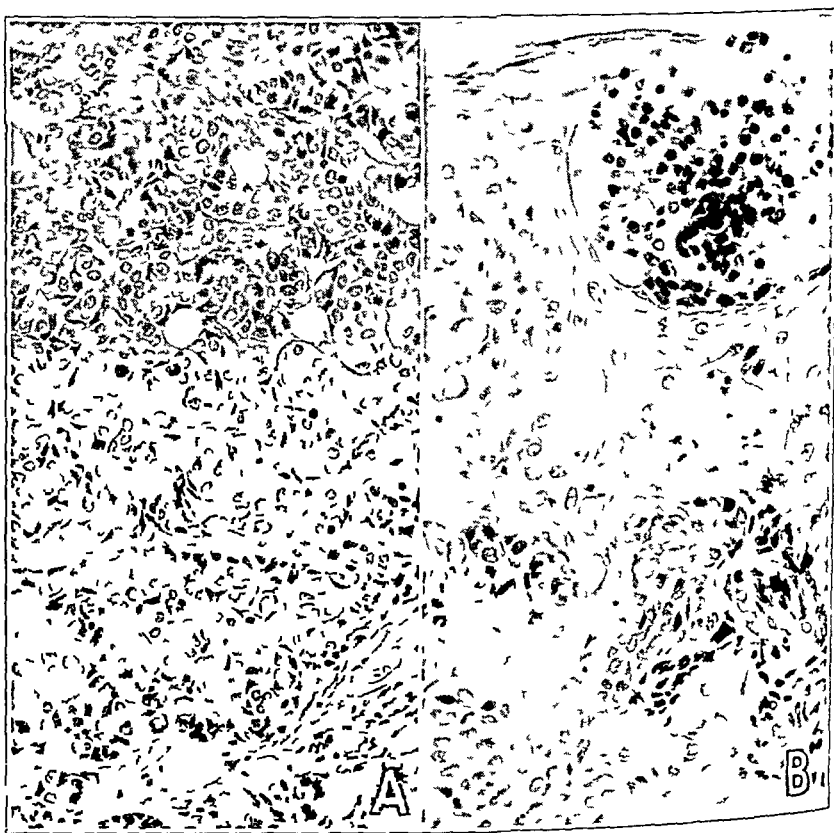


Fig 3 (case 4)—Metastatic adenocarcinoma of the scalp. *A* shows the character of undifferentiated cells, with many mitotic figures and a tendency toward formation of alveoli, *B* shows approximation to epidermis and invasion by tumor cells.

overlying skin. Rarely is a patient encountered who has discrete, sclerodermatous-like plaques independent of carcinoma en cuirasse of the breast. Lesions more than 4 cm in diameter are relatively uncommon, as is also ulceration. There are no diagnostic changes in color or in pigmentation. The lesions may be multiple or solitary.

1 Suzuki, N. Multiple Skin Metastases from Cancer of Internal Organs, *J. Cancer Research* 2: 357-388 (Oct.) 1918.

Cases of solitary metastatic lesions, with or without satellite lesions, have been reported (case 1). Microscopically, the malignant cells are usually found in the lower portions of the cutis, with extension both upward toward the epidermis and downward toward the subcutaneous tissue. Ulceration of the epidermis usually occurs as the result of pressure phenomenon rather than as the result of invasion of the epidermis by tumor cells. Proliferation of the connective tissue and inflammatory reaction in varying degrees are associated with the metastatic nodules.

When results of staining procedures for mucin are positive, the implication is that the primary carcinoma probably is situated in the gastrointestinal tract. Usual primary sites of internal carcinomas that have cutaneous metastasis are encountered, according to Gates,² in the lung in 12 per cent of the cases, in the stomach in 15 to 31 per cent, in the uterus in 9 per cent and in the kidney in 9 per cent.

Cutaneous metastasis may occur at any age, extensive cutaneous metastasis of thymic carcinoma having been reported as existing in a newborn infant.³ As a rule, metastatic lesions are encountered in patients in the later decades of life. As to the frequency of cutaneous metastasis, statistics vary from less than 1 per cent to 27 per cent of cases.⁴ Gates emphasized that although most metastatic lesions in the cases she studied were confined to the region of the growth, some tumors had a predilection for the scalp, namely, 33 per cent of carcinomas of the breast and 20 per cent of other carcinomas. The observations of Gates were substantiated by a review of the cases of cutaneous metastasis involving patients that have been seen at the Mayo Clinic, including the cases of carcinoma of the breast, which we have omitted from general discussion.

Keeney⁵ stated that metastasis in the skin is a more frequent accompaniment of carcinoma of the trachea than it is of carcinoma of the larynx or of a bronchus.

Edel⁶ said he had observed that cutaneous metastasis from cancer of the intra-abdominal organs afflicted most frequently those patients who had carcinoma of the stomach.

² Gates, O. Cutaneous Metastases of Malignant Disease, *Am J Cancer* **30** 718-730 (Aug) 1937.

³ Bedford, G. V. A Case of Carcinoma of the Thymus with Extensive Metastasis in a New-Born Child, *Canad M A J* **23** 197-202 (Aug) 1930.

⁴ (a) McWhorter, J. E., and Cloud, A. W. Malignant Tumors and Their Metastases. A Summary of the Necropsies on Eight Hundred and Sixty-Five Cases Performed at the Bellevue Hospital of New York, *Ann Surg* **92** 434-443 (Sept) 1930. (b) Gates.²

⁵ Keeney, E. L. Primary Carcinoma of Trachea with Cutaneous Carcinomatosis, *Bull Johns Hopkins Hosp* **61** 411-420 (Dec) 1937.

⁶ Edel, E. Ueber Hautmetastasen bei Magenkarzinom, *Arch f Verdauungskr* **53** 402-415 (May) 1933, abstracted, *Am J Cancer* **21** 134, 1934.

We shall now consider various conditions with which metastatic carcinomas of the scalp are most likely to be confused. The simultaneous occurrence of multiple primary neoplasms both of the skin and of internal organs is an infrequent but not a rare phenomenon, and is to be differentiated from metastatic lesions by concomitant observations.⁷ Ordinary types of basal and of squamous cell epithelioma, with their characteristic early borders, and melanoepitheliomas need only to be mentioned. With rapidly growing metastatic melanomas in which pigment is lacking, diagnosis may be difficult, clinically or pathologically. More difficult is the distinction between solitary and multiple lesions of different types of lymphoblastoma involving the scalp, lesions which may arise primarily, from the skin itself, or secondarily, as a result of extension from within. In neoplasms of any type which show a grade 4 degree of malignancy the cells may be so immature as to make it difficult to recognize or to distinguish between carcinoma and lymphosarcoma.⁸ Tauber's case⁹ may be regarded as an example of this difficulty.

SEBACEOUS CYSTS

Sebaceous cysts, either solitary or multiple, occur most frequently on the scalp, and when they are calcified or fibrotic they may closely simulate in appearance and in firmness to palpation the nodules of metastatic carcinoma. Malignant change has been reported as occurring in sebaceous cysts in from 2.2 per cent¹⁰ to 3.4 per cent¹¹ and even in 9.2 per cent¹² of the cases. In 15 per cent of such cases, basal cell epithelioma develops.¹³ The other lesions are squamous cell epitheliomas with a varying degree of malignancy. These lesions should not be regarded as precancerous in the true sense of the term.¹⁴ Sebaceous cysts must be dis-

7 (a) Hanlon, F. R. Multiple Primary Carcinomas, *Am J Cancer* **15** 2001-2012 (July) 1931. (b) Hurt, H. H., and Broders, A. C. Multiple Primary Malignant Neoplasms, *J Lab & Clin Med* **18** 765-777 (May) 1933.

8 (a) Broders, A. C. Carcinoma in Situ Contrasted with Benign Penetrating Epithelium, *J A M A* **99** 1670-1674 (Nov 12) 1932. (b) Montgomery, H. Histogenesis of Basal-Cell Epithelioma, *Radiology* **25** 8-23 (July) 1935.

9 Tauber, E. B., Goldman, L., and Barrett, C. Mesenchymoma: A New Type of Turban Tumor, *Arch Dermat & Syph* **37** 444-450 (March) 1938.

10 Stone, M. J., and Abbey, E. A. Sebaceous Cyst: Its Importance as a Precancerous Lesion, *Arch Dermat & Syph* **31** 512-515 (April) 1935.

11 Caylor, H. D. Epitheliomas in Sebaceous Cysts, *Ann Surg* **82** 164-176 (July) 1925.

12 Bishop, E. L. Epidermoid Carcinoma in Sebaceous Cysts, *Ann Surg* **93** 109-112 (Jan) 1931.

13 Collins, D. C. Carcinoma Originating in Sebaceous Cysts, *Canad M A J* **35** 370-372 (Oct) 1936.

14 Montgomery, H. Precancerous Dermatoses and Epithelioma in Situ, *Arch Dermat & Syph* **39** 387-408 (March) 1939.

tinguished also from keratomas and dermoid cysts¹⁵ Puncture of the ordinary sebaceous cyst and expression of the odoriferous contents usually establishes the diagnosis Gates² mentioned that the cutaneous metastatic lesions of renal carcinoma are most likely to be mistaken for sebaceous cysts, especially in the scalp

CYLINDROMA

The term "cylindroma" includes the endothelioma capitis of Spiegler, turban tumor of the scalp, naevus epitheliomato-cylindromatosus, naevo-epithelioma adenoides and various other names¹⁶ In its classic form of multiple pea-sized to egg-sized tumors which are limited to the scalp, the disease is not to be confused with any other condition

Cylindroma, however, can occur in the form of a solitary lesion, as Binkley¹⁷ has emphasized Of 6 instances of the condition encountered at the Mayo Clinic, in 5 there was a solitary tumor, and in 3 of these the growth involved the forehead or scalp In 1 instance there were a typical cylindroma of the scalp and a typical epithelioma adenoides cysticum of the upper lip (fig 4 *A* and *B*) Ingels,¹⁸ working with one of us (Montgomery), and others¹⁹ have emphasized that all transitions between cylindroma, epithelioma adenoides cysticum, syringoma and even adenoma sebaceum may be encountered in the same patient and even in the same lesion All four of these conditions may be regarded as benign types of basal cell epithelioma with a marked hereditary tendency,²⁰ and

15 (a) Broders, A. C and Wilson, E Keratoma A Lesion Often Mistaken for Sebaceous Cysts, *S Clin North America* **10** 127-130 (Feb) 1930 (b) Dealy, F N Wens, *Am J Surg* **36** 132-136 (April) 1937

16 (a) Ewing, J Neoplastic Diseases, ed 3, Philadelphia, W B Saunders Company, 1928 (b) Ronchese, F Multiple Benign Epithelioma of the Scalp (Turban Tumors), *Am J Cancer* **18** 875-887 (Aug) 1933 (c) Stillians, A W Nevo-Epithelioma Adenoides (Cylindroma) of the Scalp, *Arch Dermat & Syph* **27** 481-489 (March) 1933

17 Binkley, G W Naevus Epitheliomato-Cylindromatosus, *Arch Dermat & Syph* **37** 289-300 (Feb) 1938

18 Ingels, A E Epithelioma Adenoides Cysticum with Features of Syringoma, *Arch Dermat & Syph* **32** 75-85 (July) 1935

19 (a) Gans, O Naevus Epithelioma-Cylindromatosus, in *Histologie der Hautkrankheiten*, Berlin, Julius Springer, 1928, vol 2, pp 295-303 (b) Savatard, L Epithelioma Adenoides Cysticum, *Brit J Dermat* **50** 333-341 (July) 1938 (c) Schuermann, H, and Weber, K Beitrag zur Kenntnis der Spieglerischen Tumoren (Cylindrome) nebst einigen Bemerkungen zum Epithelioma adenoides cysticum, *Arch f Dermat u Syph* **175** 682-695, 1937 (d) Stillians^{16c} (e) Weidman, F D, in discussion on Stillians^{16c}

20 (a) Wiedmann, A Weitere Beiträge zur Kenntnis der sogenannten Zylindrome der Kopfhaut, *Arch i Dermat u Syph* **159** 180-187, 1930 (b) Ingels¹⁸

unless they are subjected to repeated irritation and trauma or to improper or incomplete removal they rarely, if ever, become malignant and metastasize

Although cylindroma is usually confined to the scalp, it may be encountered anywhere on the glabrous skin. Spiegler stated that such tumors are endotheliomas. Other authors have expressed the opinion that the cells are derived from sweat glands,²¹ sebaceous glands,^{16b} surface epithelium or hair follicles,²² still others have said that they are derived from undifferentiated ectoderm.²³ In several instances, one of us (Montgomery) has been able to trace the connection of a cylindroma to the basal cells of the epidermis, and in none of the cases of cylindroma



Fig 4—Cylindroma of the scalp and a lesion on the lip of the same patient. *A*, cylindroma (nevus epithelioma cylindromatosis) of the scalp, depicting lobule of small basal-like cells surrounded by hyalin-like membrane and also involutional changes of individual cells within the lobules. *B*, lesion from the lip, showing the typical picture of epithelioma adenoides cysticum and the arrangement of basal cells arising from the walls of dilated and hyperkeratotic hair follicles, as well as cystic changes.

21 (a) Davies, J. H. T. A Contribution to the Histology of the Cylindromatous Tumours of the Scalp, *Brit J Dermat* 40 241-246 (June) 1928. (b) Jones, J. W., Alden, H. S., and Bishop, E. L. Turban Tumor, or Sweat Gland Carcinoma So-Called Endothelioma of the Scalp, Report of a Case Illustrating Its Epithelial Structure, *Arch Dermat & Syph* 26 656-659 (Oct) 1932.

22 (a) Pinkus, F., cited by Stillians.^{16c} (b) Stillians.^{16c}

23 (a) Binkley.¹⁷ (b) Weidman.^{19c}

observed at the Mayo Clinic has any connection been established between cylindromas and mature sweat ducts or sweat glands

The histologic picture of cylindroma is that of a benign basal cell epithelioma. The tumor is composed of closely packed lobules and strands of cells which are surrounded by dense homogeneous hyalin-like sheaths, which Pinkus^{22a} has likened to the membrane of the outer sheath of the hair root. The cells within the lobules frequently arrange themselves in alveoli or in tubules, simulating sweat ducts and sweat glands (fig 5 A). Cystic and hyalin-like changes occur between these strands and also intracellularly. Mitotic figures are infrequent, and all the tumor cells are well formed and show no appreciable evidence of immaturity as compared with the normal basal cells of the epidermis.

CARCINOMA OF THE SWEAT AND SEBACEOUS GLANDS

Carcinoma of the sweat and sebaceous glands is among the rarest of dermatologic entities and has recently been reviewed by several authors²⁴. It is our impression, however, that many of these lesions have been classified as carcinoma of the sweat glands on the basis of the presence of so-called myoepithelium, whereas they were simply cylindromas.

In fact, Ricker and Schwalb²⁵ failed to distinguish between cylindroma and sweat gland epithelioma. Cases reported in this country by Jones, Alden and Bishop^{21b} seem to be definitely instances of cylindroma rather than of carcinoma of the sweat glands. We have yet to observe a definite case of carcinoma of the sweat glands in which by serial section or by wax reconstruction the tumor's origin from mature sweat glands could be demonstrated.

Weidman and Besancon²⁶ described an adenoma of the sweat glands occurring on the shoulder of a patient, and also epithelioma adenoides cysticum of the face. No connection could be demonstrated by serial section or wax reconstruction of the sweat gland adenoma with the

24 (a) Dupont, A. Epitheliomas sebaces multiples a point de depart epidermique, *Bull Soc franç de dermat et syph* 45 704-709 (May) 1938. (b) Favre, M., Jossierand, A., and Martin, J. F. Cancers des glandes annexes de la peau. Epitheliomas sudoripares et sebaces, in Darier, J., and others. *Nouvelle pratique dermatologique*, Paris, Masson & Cie, 1936, vol 6, pp 768-786. (c) Flarer, F. Considerations histogenetiques et cliniques sur les epitheliomes cutanes de derivation glandulaire sudoripare, *Ann de dermat et syph* 6 1073-1106 (Dec) 1935. (d) Loos, H. O. Die Carcinome der Anhangsgebilde der Haut, *Arch f Dermat u Syph* 174 465-510, 1936. (e) Muller, P. Deux cas d'epitheliome sudorifere, *Bull et mem Soc d chirurgiens de Paris* 22 741-744 (Dec 5) 1930.

25 Ricker, G., and Schwalb, J. *Die Geschwülste der Hautdrüsen*, Berlin, S. Karger, 1914.

26 Weidman, F. D., and Besancon, J. H. Histologic Differences in "Syringoma" of the Face and Shoulder, *Arch Dermat & Syph* 21 279-293 (Feb) 1930.

mature sweat glands There is a tendency to ascribe some carcinomas of the sweat glands to apocrine glands, again without morphologic proof of their origin from such glands

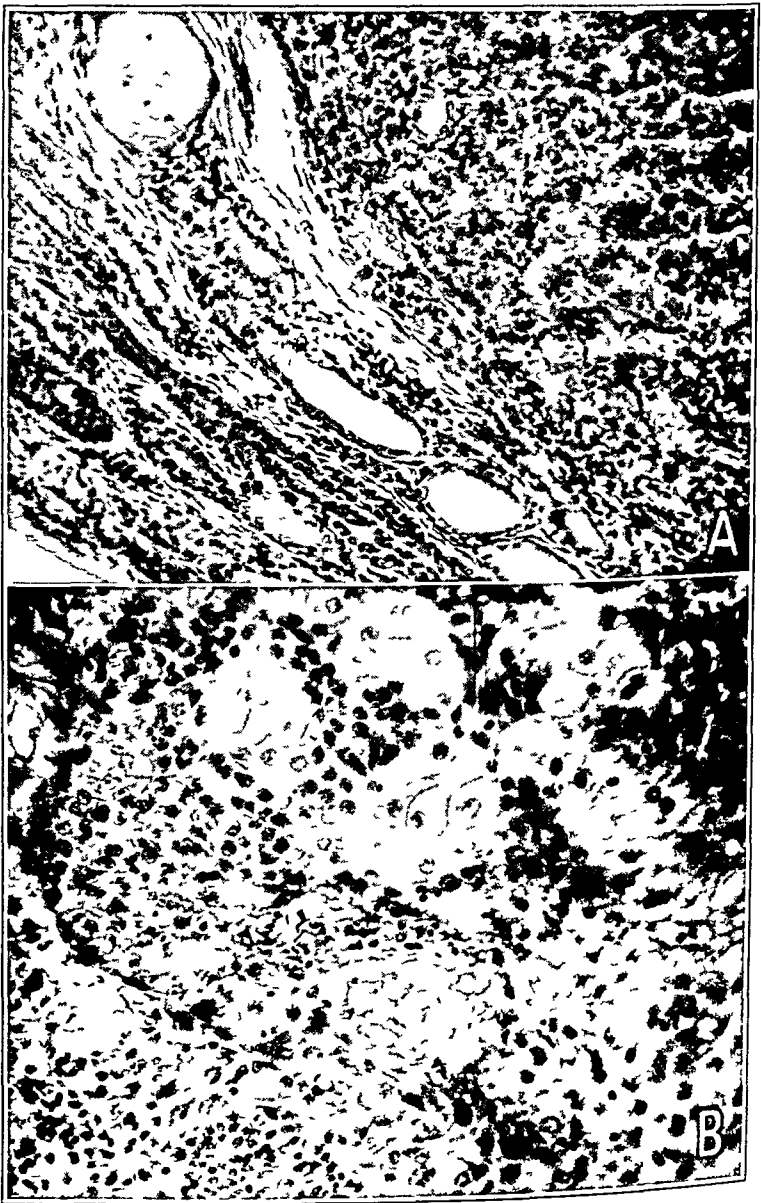


Fig 5—*A*, solitary cylindroma of the forehead, showing definite tubular and alveolar arrangement of tumor cells simulating normal sweat ducts and also hyaline changes occurring within tumor cells, *B*, carcinoma of the sebaceous gland from the midportion of the back, showing transition of sebaceous cells to undifferentiated squamous cells with many mitotic figures

Loos^{24d} mentioned that true carcinoma of the sweat glands sometimes occurs on the soles and the genitalia and in some instances merges with nevroid and hidradenoid types. Metaplasia of sweat ducts to sebaceous cells and mucous glands can occur²⁷

Loos^{24d} spoke of local recurrence following excision, but distant metastasis is known. Flarer^{24c} declared that involvement of the regional lymph glands may be found. Clinical distinction between carcinoma of the sweat glands and that of the sebaceous glands is not always possible.

Various types of lesions have been described under the term "carcinoma of the sebaceous glands." Again, those lesions of the basal cell type, called "carcinoma sebaceum baso-cellulare" by the French school, seem to be essentially varieties of ordinary basal cell epithelioma in which the basal cells¹⁸ of the epidermis or of the membrane of the sebaceous glands may also participate in the process and in which some of the basal cells tend to differentiate to sebaceous cells rather than to basal or prickle cells^{24a}. These lesions may be regarded as relatively benign, as may also those arising from sweat glands or from sebaceous glands and from meibomian-Zeiss glands, and those in relation to sebaceous nevi and sebaceous adenoma and epithelioma adenoides cysticum. Carcinomas of the sebaceous glands exhibit no diagnostic clinical features. They are usually yellowish nodules and are most frequently found in the scalp, the neck and the axillae.

We believe that Cutler's and Buschke's²⁸ estimate that adenocarcinoma has formed 2 per cent of all skin cancers probably sets too high a figure.

True carcinoma of the sebaceous glands, however, may occur as an adenocarcinoma, with or without features of squamous cell epithelioma of varying degrees of malignancy (fig 5 B). We have seen 4 such carcinomas of the sebaceous glands at the Mayo Clinic. Two of these occurred on the back of the neck, and the others occurred about the genitalia. Metastasis is of infrequent occurrence even in connection with this type of lesion.

SUMMARY AND CONCLUSIONS

1 Cutaneous metastasis of internal carcinoma may be limited to the scalp. Four cases of such metastasis are reported, in 1 of which diagnosis was established only after microscopic examination of the metastatic nodule.

2 In regard to cutaneous metastasis, certain types of internal cancer have a predilection for metastasizing to the scalp. It is important to

27 Walther, M., and Montgomery, H. Schweissdrüsentumor mit Epithelmetaplasie, *Arch f Dermat u Syph* **163** 420-426, 1931.

28 Cutler, M., and Buschke, F. *Cancer Its Diagnosis and Treatment*, Philadelphia, W B Saunders Company, 1938.

distinguish these metastatic lesions from sebaceous cysts, cylindroma and carcinoma of the dermal appendages. Such differentiation may require careful histologic study as well as consideration of the clinical history and of the course of the lesions concerned.

3 True carcinoma of the sweat glands is exceedingly rare. Many lesions diagnosed as such probably should be classified as cylindroma, which is essentially a benign lesion.

4 Careful examination of the skin of the entire body and especially of the scalp of the patient should be made in instances in which an internal malignant process is suspected. Histologic studies of the cutaneous lesions may establish a definite diagnosis without necessity for resorting to exploratory operation or other major surgical procedures.

CLINICAL CLASSIFICATION OF LESIONS OF THE LOWER EXTREMITIES ASSOCIATED WITH DIABETES

A GUIDE FOR OPERATION AND THE LEVEL OF AMPUTATION

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AND

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Lesions of the lower extremities associated with diabetes can be classified by purely clinical methods. This classification can be used as a guide for operation and will indicate which lesions

- 1 Can be treated conservatively
- 2 Require operation
- 3 Present urgent indications for treatment
- 4 May be incised safely
- 5 Will heal with amputation of the toe
- 6 Require amputation at the calf
- 7 Require amputation at the thigh

Until recently, all the lesions have been vaguely grouped under the term "diabetic gangrene." The first suggestion of classification was made by Root and McKittrick when they called attention to the fact that some lesions are vascular and some infectious. In the light of recent progress in the diagnosis of diseases of the peripheral vascular system and our own observations in many cases,¹ we have elaborated a practical clinical routine of examination. From the application of this careful examination we have derived our classification and guide for surgical procedure.

CLASSIFICATION

The lesions consist of two fundamental pathologic elements (1) arterial insufficiency (due to sclerosis) and (2) infection

¹ Williams, F W, and O'Kane, T J. Mortality in Surgical Diabetes. Criteria and Technique in Extremity Lesions, Five Year Study of Four Hundred and Ninety-Six Cases, Surg, Gynec & Obst **64** 956-963 (May) 1937. O'Kane T J, and Williams, F W. Care of Diabetic Extremity Lesions, S Clin North America **18** 369-377 (April) 1938.

To classify lesions consisting of two elements there must logically be three classes (table 1)

- 1 Purely vascular ("four plus")
- 2 Purely infectious ("four plus")
- 3 Mixed

Mixed lesions, consisting of combinations of both elements, must be considered according to the degree in which each element is present (arterial impairment and infection). We feel that arterial insufficiency is more important and therefore have arbitrarily subclassified the mixed lesions according to the degree of arterial impairment in an infected limb (table 1)

TABLE 1—*Classification of the Lesions of the Lower Extremities Associated with Diabetes*

	Criteria
Vascular ("Four plus vascular")	<ul style="list-style-type: none"> { Marked arterial insufficiency { Initial gangrene { No infection
Mixed { "Three plus vascular"	<ul style="list-style-type: none"> { Marked arterial insufficiency { Initial gangrene { Infection superimposed
Mixed { "Two plus vascular"	<ul style="list-style-type: none"> { Moderate arterial insufficiency { Initial infection { Gangrene superimposed
Mixed { "One plus vascular"	<ul style="list-style-type: none"> { Slight arterial insufficiency { Initial infection { No gangrene
Infectious ("Four plus infectious")	<ul style="list-style-type: none"> { No arterial insufficiency { Initial infection { No gangrene

A lesion presenting marked arterial insufficiency with infection is called a "three plus vascular mixed lesion"

A lesion presenting moderate arterial insufficiency with infection is called a "two plus vascular mixed lesion"

A lesion presenting slight arterial insufficiency with infection is called a "one plus vascular mixed lesion"

Clinically these lesions in the great majority of cases have typical histories and courses

CRITERIA

The criteria for the classification are as follows (table 1)

1 *Purely Vascular Lesions*—There is evidence of marked arterial insufficiency, these lesions are initially gangrenous (death of tissue in toto) and infection is not present (fig 1)

2 *Purely Infectious Lesions*—There are no signs of arterial insufficiency. The lesion is initially infectious. There is no gangrene (fig 2)

3 *Mixed Lesions*—(a) *Three Plus Vascular Mixed Lesions*. There are marked signs of arterial insufficiency with infection (fig 3). These lesions are in the great majority of cases initially gangrenous. They usually are lesions which were at first purely vascular (fig 3 A) and

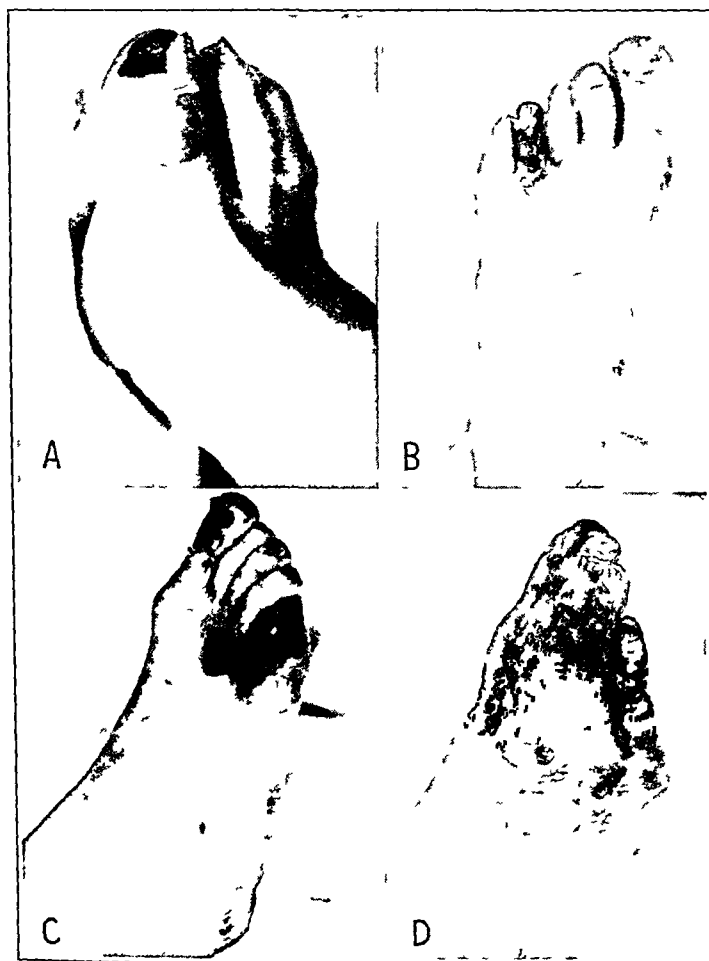


Fig 1—A, purely vascular superficial lesion B, purely vascular localized lesion C, purely vascular extensive lesion D, purely vascular, very extensive lesion

while waiting for demarcation became infected (fig 3 B). Occasionally, however, a case is seen in which there are signs of marked basic arterial insufficiency and an infection but not gangrene. In such a case there is usually adequate collateral circulation, but such cases are rare.

(b) *Two Plus Vascular Mixed Lesions*. There are moderate signs of arterial insufficiency with infection. In the great majority of these

cases, the process starts as an infection, and the edema and swelling concomitant with infection cause impairment of the collateral circulation, by compression and superimposed gangrene (fig 4)



Fig 2—Purely infectious lesion The patient was a Negro

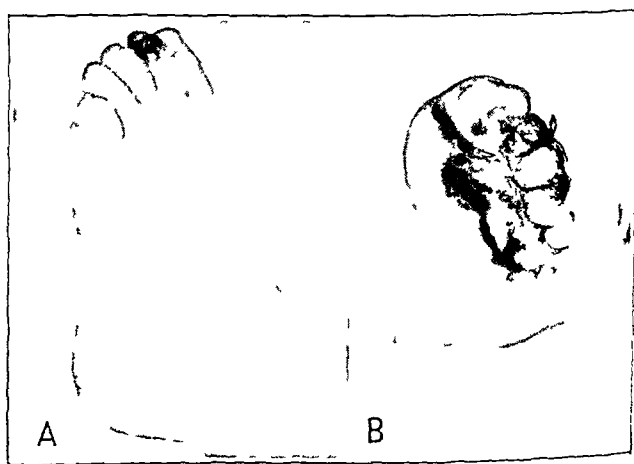


Fig 3—*A*, initial lesion, purely vascular and localized *B*, ultimate lesion "three plus vascular mixed" The infection was superimposed on the initial gangrene

(*c*) One Plus Vascular Mixed Lesions There are slight signs of arterial insufficiency with infection In the great majority of cases the process is initially an infection which progresses or heals slowly but in which gangrene does not develop (fig 5)



Fig 4—Lesion ("two plus vascular mixed") was originally an infected corn. The patient was a Negro. There was edema of the dorsum of the foot, which compressed the collateral vessels, causing gangrene (proximal).

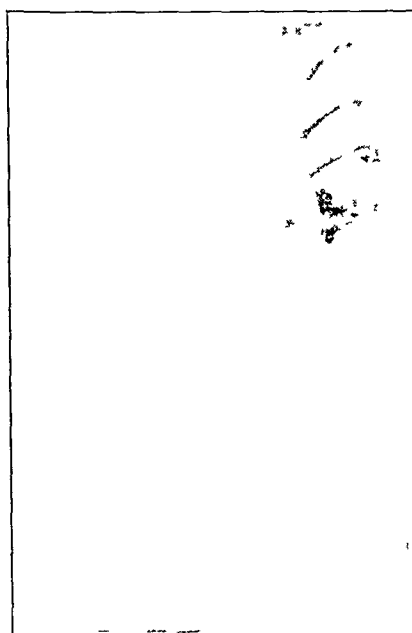


Fig 5—"One plus vascular mixed" lesion. Slight impairment of the circulation retarded the healing of an infected corn, but gangrene did not occur.

TABLE 2—*Diagnostic Criteria for Lesions of the Lower Extremities Associated with Diabetes*

Systemic Lesion	Signs and Symptoms	Character of the Observation	Classifications of Lesions					Infectious, 'Four Plus' (Purely Infectious)
			Vascular "Four Plus" (Purely Vascular)	Mixed			"One Plus Vascular"	
				"Three Plus Vascular"	"Two Plus Vascular"			
Systemic Lesion	Over 55 years	Vascular Infectious	Usually Rarely	Usually Rarely	Frequently Often	Occasionally Frequently	Rarely Usually	
	Under 55 years	Vascular Infectious	Usually Rarely	Usually Often	Frequently Frequently	Rarely Occasionally	Very rarely Occasionally	
	Concomitant disease	Vascular Infectious	Nephrosclerosis Often late	Nephrosclerosis Often	Nephritis Often	Nephritis Occasionally	Nephritis Not rarely Occasionally	
	Cerebral sclerosis	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Coronary sclerosis	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Renal lesion	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Ostitis	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Metastatic abscesses	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Vascular evidence	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Arcus senilis	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
Local Lesion	Retinal sclerosis	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Radial sclerosis	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	"J. K. G." changes	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Infectious evidence	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Temperature	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Pulse rate	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Leukocytosis	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Blood culture, positive	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Gangrene	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Infectious	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
Foot and leg	Redness	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Swelling	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Heat	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Fluctuation	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Discharge	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Pain	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Claudication	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Night pain	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Throbbing	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	
	Bone lesion	Vascular Infectious	Usually Rarely	Usually Often	Frequently Often	Occasionally	Never Rarely	

Nourishment	Usually	Usually	Usually	Often	Rarely	Never
Nails, transverse laminations						
Skin						
Liaistcity	Lost	Lost	Diminished		Normal	Normal
Dryness	Markedly	Markedly	Moderately		Slight edema	Edema
Atrophy	Markedly	Markedly	Markedly		Slight	Absent
Absence of hair	Markedly	Markedly	Markedly	Slightly	Rarely	Normal
Muscle and fat, atrophy					None	None
Lymphatics					Occasionally	Occasionally
Ducts infected	Frequently	Frequently	Often		Occasionally	Occasionally
Enlarged glands	Frequently	Frequently	Often		Occasionally	Occasionally
Tender glands						
Arterial						
Thickening						
Femoral	Markedly	Markedly	Moderately		Mild	Never
Popliteal	Markedly	Markedly	Moderately		Mild	Never
Dorsalis pedis	Markedly	Markedly	Moderately		Mild	Never
Posterior tibial						
Pulsations, diminution						
Femoral	Markedly	Markedly	Moderately		None	None
Popliteal	Markedly	Markedly	Moderately		None	None
Dorsalis pedis	Absent	Markedly	Markedly		Slightly	None
Posterior tibial	Absent	Absent	Markedly		Slightly	None
Surface temperature						
Vascular and infectious	Infected heat	Infected heat	Infected heat		Infected heat	Infected heat
Vascular	Prolonged	Prolonged	Slowed		Normal	Normal
Color changes						
Elevation pallor	Marked	Marked	Mild		No change	No change
Dependency rubor lividity	Extensive	Extensive	Limited		Slightly	No change
Capillary circulation	Delayed	Delayed	Fair		Fair	Good
Wound culture						
Staphylococcus	Negative	Occasionally	Frequently		Commonly	Commonly
Streptococcus	Negative	Commonly	Commonly		Occasionally	Occasionally
B. coli	Negative	Rarely	Rarely		Frequently	Frequently
B. Welchii	Negative	May occur	May occur		May occur	May occur
Roentgen findings						
Calcified vessels	Usually	Usually	Frequently		Rarely	Never
Bone necrosis	Rarely	Rarely	Occasionally		Frequently	Often

Thus, it is readily understood that the lesions occurring in diabetic extremities may be simply classified according to the degree of arterial impairment and infection and the course of the lesion

CLINICAL ROUTINE

Table 2 is an outline of the routine clinical examination by which we determine the degree of arterial impairment and the severity and extent of the infection. Under "Signs and Symptoms" we have tabulated the clinical observations made routinely in our cases. These include systemic and local findings. The important systemic findings are age, concomitant disease and evidences of sclerosis and infection. The local findings include all clinical observations of the lesion and of the foot and leg for study of the vascular and infectious condition. The center column indicates whether the observation is for a vascular or for an infectious lesion. These observations have been tabulated against the classification. In the vertical columns, under each class of lesion is an adverb of degree giving a conception of the frequency of occurrence of the finding. If one reads each column of the table from the top down, under each class one reviews a series of clinical observations, and these form a definite clinical concept which fits the classification. In this manner, we are able clinically, without instruments, to arrive at a definite conclusion as to the degree of arterial insufficiency and the severity and extent of infection.

GUIDE FOR SURGICAL TREATMENT

In considering surgical treatment of lesions of the lower extremities, we feel that the classification given serves as an excellent guide. When operation is indicated, it must be done only at a level where the circulation is competent to cope with the trauma of operation. The severity and extent of the infection must also be considered in deciding which procedure is indicated.

With these concepts in mind, the classification may be considered a guide for operation (table 3).

The great majority of purely vascular superficial lesions (fig 1 *A*) do well without operation. Great care must be taken to avoid infection. These lesions take a long time to heal but do heal eventually.

With purely vascular lesions which are localized (fig 1 *B*) to a toe or to part of a toe, there is no urgency if they remain uninfected. If they do not show signs of demarcation and autoamputation after a sufficient time amputation is indicated. The circulation will not permit amputation of the toe, however. The level of the calf or that of the thigh must be selected, depending on the results of circulatory examination of the limb. For the extensive (figs 1 *C* and 1 *D*) purely vascular lesions, if they extend above the base of the toe (fig 2), prompt amputation

at the calf or at the thigh is indicated, the level of amputation depending on the circulation

For the purely infectious lesions, with the basic circulation good, the surgical indications are quite different. Superficial, localized and spreading infections are treated by conservative methods or by incision and drainage. This must be carefully done to avoid trauma, maintain circulation and assure drainage.

To the mixed types of lesions the same principles apply. The infected area must be drained or removed and the circulation must be adequate to withstand the trauma of operation and to facilitate healing. The three plus vascular mixed lesions (fig. 3) are the most dangerous. There is marked vascular impairment together with infection, and there-

TABLE 3—*Surgical Procedures in the Light of the Classification of Lesions of the Lower Extremities Associated with Diabetes*

Classification	Character of Lesion	Surgical Procedures
Vascular		
Four plus vascular'	Superficial Localized Extensive	No operation Amputation at calf if collateral circulation is good Amputation at thigh (urgent)
Mixed		
Three plus vascular''	Spreading	Amputation at thigh (urgent)
"Two plus vascular"	Spreading	Amputation at calf (urgent)
"One plus vascular"	Superficial Localized Spreading	No operation Incision and drainage amputation of toe Amputation at calf (urgent)
Infectious		
"Four plus infectious"	Superficial Localized Spreading	No operation Incision and drainage Incision and drainage (urgent)

fore amputation at the thigh is urgently required. The two plus vascular mixed lesions (fig. 4), because of the better circulation, can in most cases be amputated at the level of the calf. The only exception occurs when the infection has already spread to the calf, in such a case, amputation at the thigh is indicated. The one plus vascular mixed lesions when superficial (fig. 5) may heal under conservative treatment. If localized, they sometimes require incision or amputation of the toe. If spreading, they require amputation at the level of the calf.

These indications are all shown in table 3. The basic principle is an estimation of the degree of arterial insufficiency and the severity and extent of infection.

SUMMARY

Lesions of the lower extremities associated with diabetes can be clinically classified without instrumental observations. This classification is based on the degree of arterial insufficiency and the severity and extent of infection and serves as a guide for operation and the level of amputation.

PERSISTENCE OF MECKEL'S DIVERTICULUM

REPORT OF A CASE

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READING, PA

Persistence of Meckel's diverticulum is exceedingly infrequent. Indeed, American textbooks on surgery never mention it. Barrington Ward,¹ however, has given an excellent description of the condition. Because of its infrequency as well as its apparently total omission in American textbooks on surgery, I consider it well worth while to present the following case.

History—W S, a boy aged 3 months, was admitted to the Reading Hospital June 14, 1939. The chief complaint was that the umbilicus had never healed and that a bright red lump shaped like a cherry was present. A brown fecal discharge was constantly present, so that a bandage was necessary all the time.

The previous medical history was irrelevant. The child had been born by normal spontaneous labor. He took his feedings well. He was given cow's milk and goat's milk with his breast feeding at night. His growth and gain in weight had been normal. There was no vomiting, and the bowels moved well.

Examination—The baby was generally well nourished and did not appear ill. The head was symmetric, with no tenderness. The aural canals were clean. The scleras were clear, the pupils were round and equal and reacted to light. There was no nasal discharge or nasal obstruction. The gums were of good color. There were no teeth. The tongue was clean and the pharynx not injected. There was no adenopathy. The chest was symmetric, the expansion was good and was equal on the two sides. The breath sounds seemed normal, with no rales. The heart did not seem enlarged, and the sounds were of good quality, with no murmurs. The abdomen generally was of normal size and shape. Peristalsis was active and normal. There were no areas of tenderness. The liver and spleen were not palpable. At the umbilicus there was a moist, bright red, cherry-shaped firm mass. From a small dimple in the mass there exuded a thin greenish brown discharge with a fecal odor. The external genitalia and the extremities appeared normal.

The urine was normal. A complete blood count showed hemoglobin, 75 per cent, red cells, 3,760,000 per cubic millimeter, white cells, 8,950 per cubic millimeter, color index, 1, polymorphonuclears, 41 per cent, and small mononuclears, 59 per cent.

Diagnosis—A tentative diagnosis of persistence of Meckel's diverticulum, patent throughout and at either end, was made.

A no. 8 soft rubber catheter was easily inserted into the dimple in the umbilical mass. Approximately 50 cc of a thin solution of barium sulfate was injected into

1 Barrington-Ward, L. *The Abdominal Surgery of Children*, ed 2, London: Oxford University Press, 1937, pp 21-23 and 257-273.

the catheter with great ease and with no sign of obstruction. A lateral as well as an anteroposterior roentgenogram was taken (see accompanying illustration).

Operation—Local anesthesia was induced and was aided by a whisky and sugar pacifier. At the beginning of the operation the dimple-like opening in the mass was ligated. A circular incision was made in the skin of the umbilicus, close to its junction with the red mass of everted diverticulum. The diverticulum was cautiously separated from the umbilical tissue and was easily pulled up approximately 2 to 2½ inches (5 to 6.3 cm) to a point where it came off from the ileum at right angles from the convex portion of the bowel. The diverticulum was removed by clamp and cautery, and the base was doubly ligated. The bowel was dropped into the peritoneal cavity. The abdominal opening was closed transversely with interrupted sutures. The skin was closed with three Michel clips.

Pathologic Examination—*Macroscopic Picture*. The specimen consisted of a piece of tissue removed from an umbilical opening. The specimen was in the form of a tube measuring 5 cm in length by 1.4 cm in diameter, to one end of which



A, lateral roentgenogram of a child with a persistent Meckel diverticulum
B, anteroposterior view

was attached a circular piece of skin 3.5 cm in diameter and 0.8 cm in thickness. The outer surface of the tubular portion was covered by serosa and contained a lumen which was patent to a probe. The inner surface resembled mucous membrane. There was no gross evidence of pathologic change.

Microscopic Picture. Transverse sections of the tubular portion of tissue showed it to be composed of serosa, two layers of muscularis, submucosa and mucosa. All the layers were intact. There was moderate congestion of the muscularis and of the serosa. The lumen contained a mucoid secretion and some cellular debris. There was no evidence of inflammatory or malignant change. The diagnosis was patent vitelline duct.

Postoperative Course—The convalescence was entirely uneventful. The patient was discharged from the hospital July 1. The general condition was excellent, and the wound was entirely healed. At the time of this report, one and a half months after discharge from the hospital, the child continues to be normal.

EFFECTS OF PRESSURE ON TISSUES

BARNEY BROOKS, M D

AND

GEORGE W DUNCAN, M D

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The fact that varying degrees of tension exist within the tissues under normal conditions is obvious from the general knowledge of such phenomena as the gaping of wounds and the protrusion of tissues through defects in the capsules of organs or enveloping sheaths of fascia. The fact that secretions of the organs may accumulate to the point of considerable tension in a reservoir such as the gallbladder or the urinary bladder is well known to every surgeon. The degree of tension existing within the vascular system and the intracranial cavity is a well known measure of differentiation between health and disease. To appreciate the fact that relatively great pressure is at times exerted on living tissues under normal conditions, it is only necessary to realize that when walking a man weighing 185 pounds (84 Kg) exerts on the soles of his feet from the weight of the body alone a pressure in excess of that needed to support a column of mercury 500 mm in height.

That pressure applied from without or developing from within living tissues is the cause of pathologic changes is illustrated by the devastating destruction associated with decubitus ulcer or by the atrophy or absorption of tissues about progressively enlarging tumors. The rapid development of alterations of tension within the tissue is presumably responsible for the pain associated with many infectious lesions, and the increase of tension in tissues enclosed by rigid fascia to approximate diastolic blood pressure is probably responsible for the throbbing of a felon.

Not only is pressure an important factor in many of the diseases of particular interest to the surgeon, but it is almost a universal accompaniment of surgical therapeutics. Every surgeon is familiar with the possibility of pressure sores resulting from the application of plaster dressings and with the distressing condition known as Volkmann's ischemic contracture which may be produced by the encircling bandage too tightly applied. He should also be aware of the fact that every suture, every ligature and every use of an artery forceps or retractor results in the application of pressure to living tissue.

Another phenomenon in clinical surgery which has frequently been of interest is the apparent great difference in the effects of the same

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amounts of pressure applied to free and to pedicle skin transplants. For example, in a routine radical operation for carcinoma of the breast, in which both free and pedicle skin transplants are used in the same wound, the amount of pressure necessary to preserve a piece of free transplanted skin often causes necrosis of the transplant which remains attached to the thoracic wall. The fact that this phenomenon has been observed by others is indicated by the presentation of a paper at a recent meeting of the American Surgical Association, in which it was stated that with large scalping wounds in which the uplifted skin is attached by a small pedicle the replaced flap of skin stands a better chance of survival if all the pedicle is divided.¹

In spite of, or perhaps because of, the facts that pressure, tension, stress and strain are always present in living tissues and often are an obviously influential factor in the production of disease and that they universally accompany the therapeutic methods peculiar to surgery, little has been written on this subject. Hunter² was aware of certain pathologic changes resulting from pressure and was sufficiently interested in the subject to preserve in the museum specimens illustrating the conclusions which he had reached. He attempted to differentiate the effects of pressure applied from without from the effects of pressure applied from within. He stated that pressure applied from within produces atrophy of tissues, in sharp contrast to the hypertrophy of tissues which follows application of pressure from without. He mentioned as an example of the former the atrophy of tissues about a growing tumor. As an example of the latter he referred to the formation of calluses and bursae at the sites of external application of pressure. He recognized that extraordinarily prolonged applications of pressure from without might produce necrosis or atrophy.

Paget³ discussed Hunter's ideas concerning the effects of pressure and stated that this was a rare instance in which Hunter was wrong. Paget stated the belief that it is not the direction in which pressure is made but the constancy of its application which determines its effect and that intermittent pressure produces hypertrophy and constant pressure produces atrophy. It just so happens, he stated, that intermittent pressures are usually from without, while constant pressures are usually from within.

The effects of pressure per se on certain physiologic processes have been studied extensively. Cattell⁴ reviewed the previous literature

¹ Farmer, A. W. *Ann Surg* **110** 951, 1939.

² Hunter, J. *The Complete Works of John Hunter*, edited by J. F. Palmer, Philadelphia, Haswell, Barrington & Haswell, 1841, p. 441.

³ Paget, J. *Lectures on Surgical Pathology*, ed. 3, Philadelphia: Lindsay & Blakiston, 1865.

⁴ Cattell, M. *Biol Rev* **2** 441, 1936.

dealing with the physiologic effects of pressure on tissue in experiments under conditions in which the effect produced could be attributed only to pressure and not to the interference with receipt or elimination of the products of cell metabolism. The experiments were performed on isolated tissues, enzymes and unicellular organisms. The pressures used were applied through a fluid medium, and a pressure of 250,000 pounds (113,500 Kg) to the square inch was necessary in some experiments to produce significant change in cell function.

Rabl⁵ applied external pressure to the long bones of rabbits by means of springs and rubber bands. He obtained resorption of a thin layer of underlying cortex and a formation of bone adjacent to this area of pressure resorption. The amount of pressure applied was not measured.

The transmission of pressures from the surface to the deeper tissues was a matter of interest in the development of the present method of measurement of blood pressure in clinical medicine. Von Recklinghausen⁶ called attention to the relation between the surface area to which the pressure is applied and the depth of its transmission and thus explained the fallacy of the high blood pressure estimations previously made with narrow cuffs.

Larsen⁷ performed experiments in which it was shown that massive necrosis of the shaft of bone could be produced by measured increase in intramedullary pressure. These experiments indicate the possibility that increased intramedullary pressure resulting from an acute infectious process is an important factor in determining the characteristic pathologic changes associated with acute osteomyelitis.

The present experiments were undertaken for the purpose of determining the influence of known amounts of pressure applied for measured lengths of time on various specific tissues in living animals.

MATERIAL AND METHOD

The experiments were performed on the tail of the albino rat for the following reasons:

- 1 The animal may be easily restrained so as to permit the application of known pressures for relatively long periods of time.
- 2 The rat's tail is remarkably uniform in shape, diameter and length.
- 3 The small thickness of the rat's tail permits the transmission, with little loss, of surface pressures to the deeper structures.
- 4 The rat's tail gives an opportunity of studying the effects of pressure on skin and its appendages, subcutaneous tissue, muscles, tendons, fascia, ligaments, bone, cartilage, blood vessels and nerves (fig 1).

5 Rabl, C R H. *Arch f klin Chir* **145** 515, 1927.

6 von Recklinghausen, H. *Arch f exper Path u Pharmacol* **46** 78, 1901.

7 Larsen, R M. *Ann Surg* **108** 127, 1938.

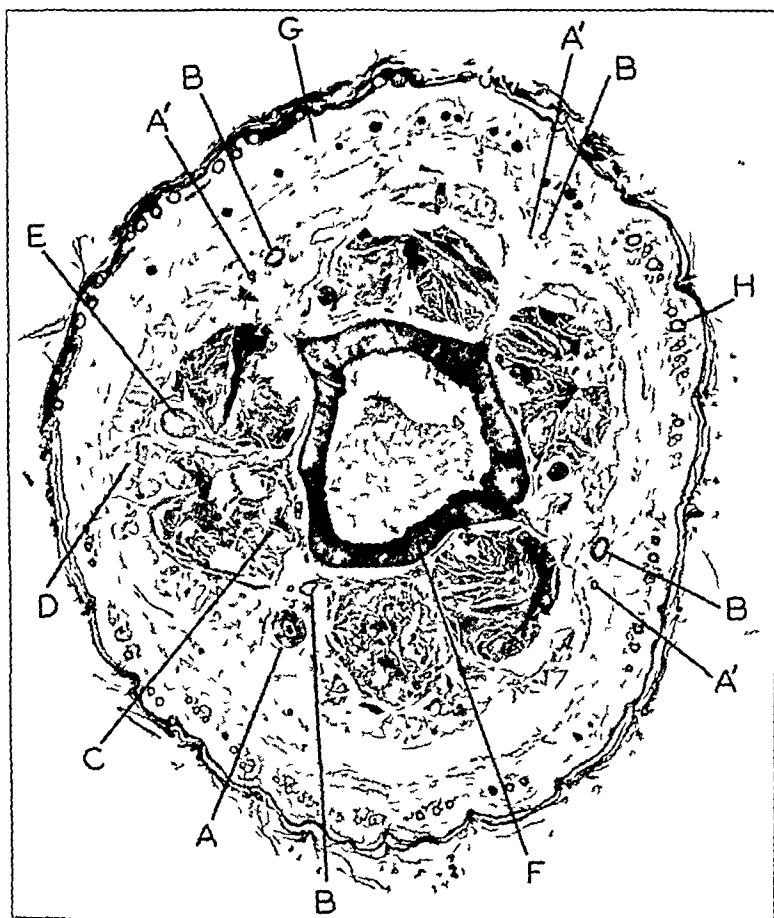


Fig 1—Photomicrograph of a cross section of the rat's tail, showing the normal anatomic relation, *A* represents a large ventral artery, *A'*, small lateral and dorsal arteries, *B*, veins, *C*, muscle, *D*, tendon, *E*, nerve, *F*, caudal vertebra, *G*, skin, *H*, hair follicle and sebaceous glands

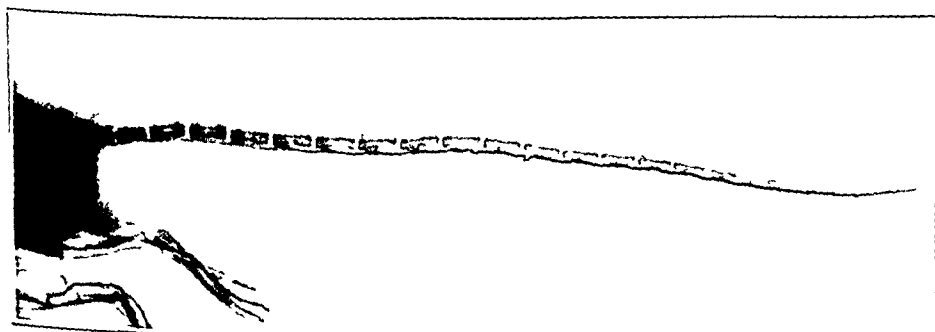


Fig 2—Roentgenogram of the arteries in the normal rat's tail. The abdominal aorta was injected with a suspension of barium sulfate. Note the large ventral artery and the smaller dorsal artery. The two lateral arteries are visible in the anteroposterior view.

5 The anatomy of the blood supply to the rat's tail is not complex (fig 2) The only part of the rat's tail to which presumably surface pressure could not be applied is that portion within the caudal vertebra

6 The rat's tail is particularly suitable for both gross and microscopic examination

7 Blood pressure in the rat's tail has been determined in a large number of experiments by Williams, Wegria and Harrison⁸ and found to be remarkably constant, ranging between 110 and 130 mm of mercury

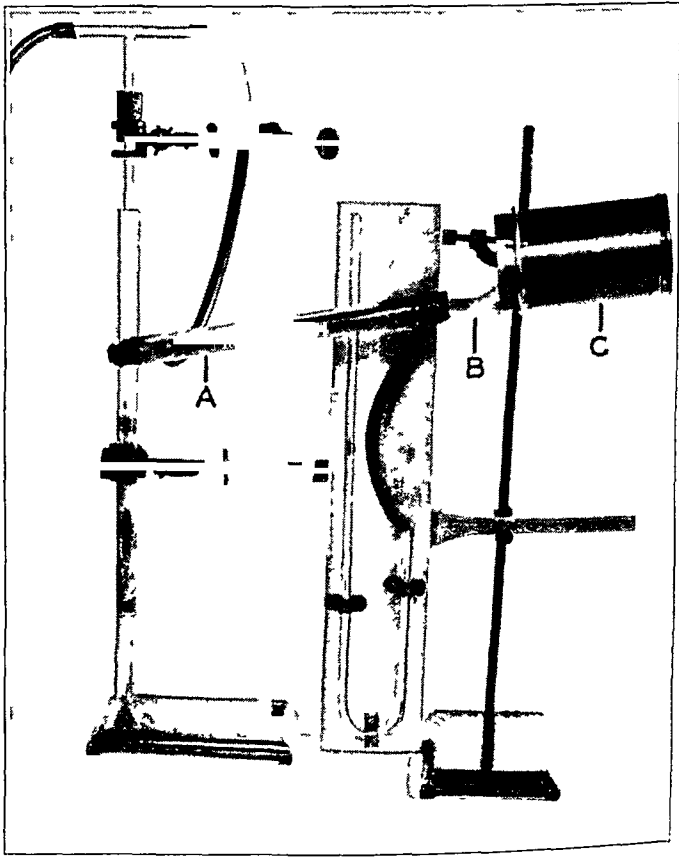


Fig 3—Photograph of the apparatus for application of continuous pressure *A* represents the plethysmograph, *B*, the rat's tail, *C*, the rat holder. In the experiments a greater length of the rat's tail was in the plethysmograph than is shown in the photograph

The animals employed weighed from 115 to 170 Gm. They were restrained in a holder similar to that described by Williams, Harrison and Grollman.⁹ The

8 Williams, J. R., Jr., Wegria, R., and Harrison, T. R. The Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, *Arch Int Med* 62: 805 (Nov.) 1938

9 Williams, J. R., Jr., Harrison, T. R., and Grollman, A. *J Clin Investigation* 18: 373, 1939

holder consisted of two telescoping brass cylindric cups, in the bottom of one of which there was a hole through which the rat's tail protruded. The bottom of the other cup was formed by copper screening. The pressure was applied to the tail by means of a plethysmograph consisting of a tube similar to the outer jacket of a Liebig condenser, through which was passed a thin-walled rubber tube securely attached at each end. Two side connections were provided, one for a mercury manometer, the other leading to a supply of compressed air through a mercury column valve for maintenance of constant pressures over long periods. After the rat's tail had been placed within the rubber tube, pressure was applied by admission of air to the space between the glass and the rubber tube (fig. 3).

One hundred and fifty experiments were performed. The pressures applied varied from 20 to 1,419 mm. of mercury. The periods for which pressure was applied varied from three to forty-eight hours. After removal of the rats from the apparatus, the animals were observed for periods as long as three months. Microscopic sections have been obtained from the various stages of pathologic change observed.

RESULTS

The pathologic changes produced were uniform in character but varied somewhat in time of appearance. The gross changes produced varied from slight redness of the distal portion of the tail through various degrees of swelling and ulceration to massive necrosis and spontaneous amputation.

The purpose of the first group of experiments was to determine the minimum time and pressure required to produce massive necrosis in every instance. This result was considered a standard from which the nature of subsequent experiments could be determined.

In these experiments healthy animals were used, and an attempt was made to prevent prolonged experiments from seriously interfering with the nutrition of the subjects. Particular care was taken to prevent dehydration by providing an adequate supply of water, and all of the experiments were carried out at room temperature.

The results of the experiments summarized in the accompanying table show that a pressure of 130 mm. of mercury applied for eighteen hours produced massive necrosis in every instance. If the same pressure was applied for seventeen hours, gangrene was produced in 7 of 9 experiments. If the pressure was reduced to 120 mm. and applied for seventeen hours, massive gangrene occurred in 2 of 5 experiments. Massive gangrene was not produced by any pressure applied for less than seventeen hours.

Gangrene of the entire tail was also produced in every instance by maintaining a pressure of 100 mm. of mercury for forty-eight hours. A pressure of 80 mm. for forty-eight hours produced gangrene in 4 of 7 experiments.

In the experiments in which gangrene was produced in seventeen or eighteen hours, the rat's tail showed some discoloration at the time of removal from the plethysmograph (fig 4 *A*). After a few hours a progressively increasing edema appeared, and in some instances areas of ulceration appeared during the first two or three days, after which the tail began to show evidence of desiccation, usually beginning at the tip (fig 4 *B*). The time required for complete dry gangrene and spontaneous separation varied from three to eighteen days.

In animals in which gangrene was produced in forty-eight hours by a pressure of 100 mm of mercury the tail appeared more discolored

Results of Pressure of Varying Degree and Duration

Number of Animals	Number of Hours Applied	Pressure Mm Hg	Hyperplasia of Epidermis	Necrosis of Distal End of Tail	Necrosis of Entire Tail
1	3	220	0	0	0
1	4	120	0	0	0
1	4	580	0	0	0
1	4	1 419	1	0	0
1	8	90	1	1	0
1	8	180	1	1	0
3	10	110	3	0	0
1	12	100	1	1	0
1	14	70	1	1	0
5	14	80	5	5	0
1	14	160	1	1	0
1	16	160	1	1	0
5	17	120	2	3	2
1	17	160	1	1	0
9	17	130	2	2	7
6	18	70	6	6	0
11	18	80	10	10	1
3	18	110	3	3	0
6	18	120	4	4	2
15	18	130	0	0	15
1	18	160	0	0	1
1	20	70	1	1	0
4	24	80	3	3	1
4	24	100	3	3	1
1	30	80	0	0	1
1	36	80	0	0	1
4	36	100	2	2	2
1	48	20	1	1	0
7	48	80	3	3	4
14	48	100	0	0	14

at the time of removal, and less edema developed. The average time required for desiccation and spontaneous amputation was approximately the same as in the experiments in which a pressure of 120 to 130 mm was applied for seventeen to eighteen hours.

In some experiments in which the factors of pressure and time had been adequate to insure the development of gangrene it was found that the tail would bleed if sectioned at the tip as long as forty-eight hours after removal from the plethysmograph. In 5 experiments in which the rat's tail had been subjected to the standard conditions for insuring the production of massive gangrene, the animals were killed immediately twenty-four hours and forty-eight hours after removal from the pleth-

mograph and the abdominal aorta was injected with a suspension of barium sulfate in water. Roentgenograms of the tail showed in each instance all of the major arteries of the tail patent (fig. 5)

The pathologic changes resulting from the application of pressure for periods insufficient to produce massive necrosis of all the tissues are

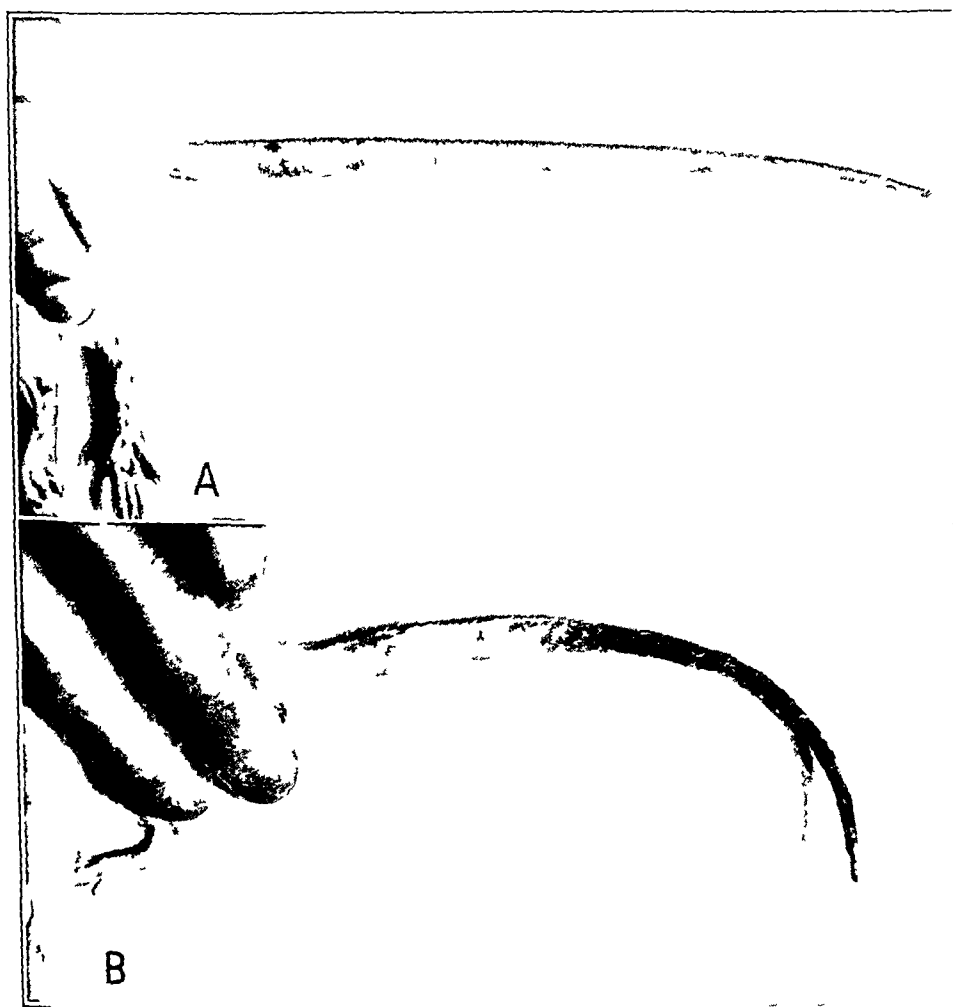


Fig. 4—*A*, photograph of the rat's tail immediately after removal from the plethysmograph. A pressure of 130 mm of mercury had been applied for eighteen hours. There is only slight discoloration. The part of the tail subjected to pressure subsequently became gangrenous. *B*, photograph of the rat's tail two days after removal from the plethysmograph in the same experiment. Note the extensive dry gangrene. Spontaneous amputation subsequently occurred.

of equal importance and perhaps greater interest than determination of the time and pressure necessary to produce massive gangrene.

Excessive pressures, e g, 1,419 mm of mercury, may produce evidences of slight damage to the tissues in as short a time as four hours, but in general it may be said that pressures considerably in excess of arterial tension, e g, 200 mm of mercury, may be applied for as much as six hours without producing any gross anatomic change other than a period of hyperemia and slight edema. If, however, pressures in excess of 70 mm of mercury are applied for periods longer than twelve hours, unmistakable anatomic pathologic changes almost universally result, although the distribution of these changes among the several tissues and the degree of change in any one tissue are not constantly produced by a particular combination of pressure and duration of application.

Perhaps the most constant change observed in these experiments was epithelial hyperplasia in both the epidermis and the cutaneous appendages, producing greatly increased scaling and the formation of

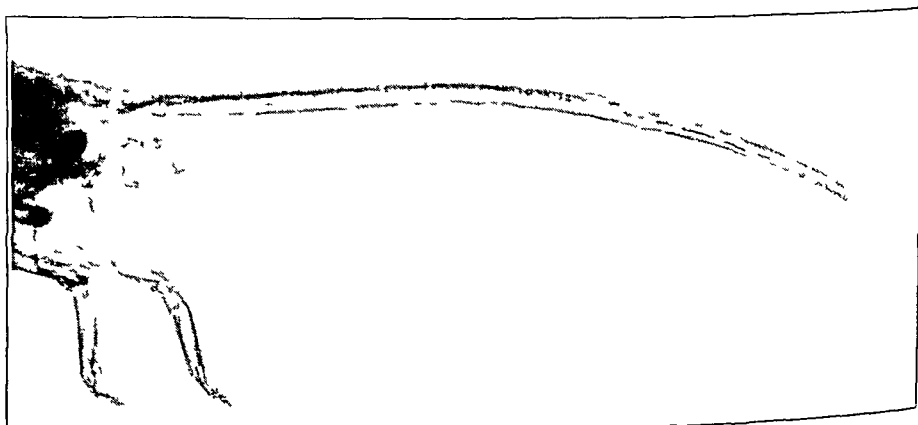
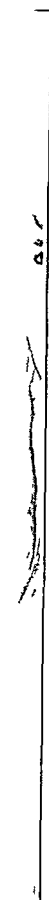


Fig 5—Roentgenogram of the rat's tail in an experiment in which the aorta was injected with a suspension of barium sulfate forty-eight hours after removal of the tail from the plethysmograph, in which a pressure of 130 mm of mercury had been applied for eighteen hours. Note that the injection mass has filled the three largest arteries approximately the same as a similar injection in a normal control animal (shown in figure 2).

thick crusts. After exfoliation of the crusts the tail lost its natural cutaneous markings and became slick. Microscopic sections showed a marked increase in the thickness of the epithelium of the skin, hair follicles and sebaceous glands. The epithelial cells showed the usual changes accompanying an active hyperplasia. The changes in the epithelium were most marked in the experiments in which the factors of pressure and time were only slightly short of those necessary to produce gangrene (fig 6).

The changes produced in muscle were of particular interest because of their bearing on the previously debated pathogenesis of ischemic contracture following the application of constricting dressings or liga-

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equally to all of its structures. In 2 experiments the successive stages of the development of fibrosis, for the most part confined to the muscles, were studied in portions of the tail removed at intervals after the applica-

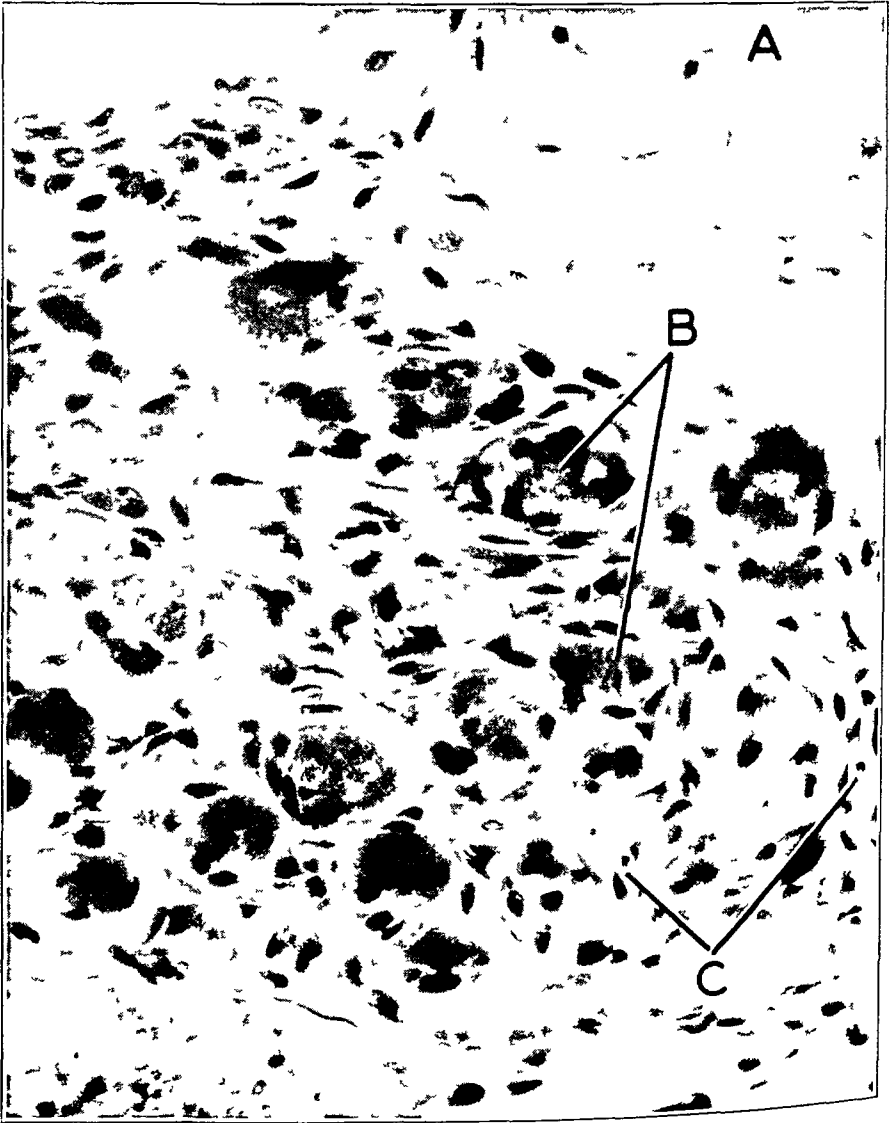


Fig 7—Photomicrograph showing replacement of muscle by fibrous tissue. *A* represents a tendon, *B*, degenerating muscle cells, *C*, fibrous connective tissue. Section was made eleven days after subjection to a pressure of 160 mm of mercury for fourteen hours.

tion of pressure. The most marked muscle fibrosis was observed in experiments in which pressure was applied for fourteen to sixteen hours. In such experiments it was observed that the rats' tails were apparently

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The results obtained in these experiments in which anemia was produced by direct pressure on tissues bear a definite relation to the results of the experiments of one of us (Brooks¹⁰), in which the effects on muscle of anemia produced by tourniquets and ligations of arteries and veins were studied. It was found that gangrene was produced in a dog's leg by the application of a tourniquet for seventeen hours and that fibrosing myositis could be produced in a single muscle by venous obstruction if there was no arterial obstruction. This pathologic change was concluded to be initiated by capillary damage produced by greatly increased intracapillary pressure. It was also concluded that fibrosis could be produced by temporary complete anemia if the period of anemia was just long enough to produce capillary damage. It was pointed out, however, that the relatively small difference in the duration of arterial obstruction required to produce selective capillary damage and that in which massive necrosis would ensue and the ease with which sclerosing myositis could be produced experimentally by obstruction of veins made it seem most likely that most of the ischemic contractures observed in clinical practice would be produced by the latter method.

CONCLUSIONS

The results of the experiments described in this paper justify the following statements. It is worth emphasizing again that these experiments deal only with the temporary application of pressure for periods of less than forty-eight hours, after which all pressure is removed.

1 Pressures comparable to those developing spontaneously within or commonly applied from without the living animal produce pathologic changes not because of pressure per se but because of obstruction of the circulation.

2 The period of viability of tissues rendered completely anemic by pressure under the usual conditions of health, temperature and maintenance of normal nutrition of the animal is remarkably constant at seventeen to eighteen hours.

3 With the application of pressures sufficient to produce pathologic changes, the duration of the pressure is of more importance than its amount.

4 Pressure only slightly below that necessary to render a part totally anemic may result in massive necrosis if the time of application is prolonged. In general, the prolongation of time necessary to produce this result is relatively greater than the diminution of pressure.

10 Brooks, B. Pathologic Changes in Muscle as a Result of Disturbances of Circulation. An Experimental Study of Volkmann's Ischemic Paralysis, *Arch Surg* 5 188 (July) 1922.

to take place. The changes in plasma volume were determined by the technique of Gibson and Evelyn³

RESULTS

A Decompression by Suction—The loss of plasma after four to five hours of distention at a pressure of 20 cm of water in a group of 7 dogs (previously reported on) averaged 35 per cent¹. Maintenance of the same level of intraluminal pressure thereafter was accompanied by a continuing loss of plasma, which reached 55 per cent of the initial volume shortly before death.

In experiment 1 of the present series (see accompanying table, section A) the loss of plasma after four hours of distention at a pressure of 20 cm of water equaled 35 per cent, but at the end of a subsequent thirteen hour period of decompression by suction the loss of plasma was 18.7 per cent of the initial volume, showing a partial recovery of the plasma lost during the period of distention. Experiments 2 and 3 of this group showed similar, though less striking, results. During the period of decompression in these 2 dogs, which lasted some fourteen hours, there was an additional average loss of 5.9 per cent in plasma volume, which compares favorably with the loss in dogs with no distention and which is in contrast to a 20 per cent additional average loss after a similar interval in dogs with continuous distention (chart 1).

To emphasize the direct relation between loss of plasma and intraluminal pressure, the initial degree of distention was reestablished for about six hours. The loss of plasma immediately after this second period of distention in 2 of the 3 dogs totaled 50 per cent. The third dog died before a measurement could be made.

B Partial Decompression by Spontaneous Deflation—In this group of 7 dogs (section B of table) a constant intraluminal pressure of 20 to 25 cm was maintained for about four hours (except in experiment 6, in which only 2 feet [60 cm] of ileum was distended and the distention maintained for seven and one-half hours). The cannula leading to the ileum was then clamped, and the intestine was allowed to resorb the trapped air. In experiments 7 and 8 the dogs breathed pure oxygen to facilitate more rapid absorption of nitrogen from the bowel.⁴ The intraluminal pressure invariably showed a rapid decline, usually to about 10 cm of water, but complete decompression was not achieved.

³ Gibson, J. G., and Evelyn, K. A. Clinical Studies of the Blood Volume. IV. Adaptation of the Method to the Photoelectric Microcolorimeter, *J. Clin. Investigation* **17**: 153, 1938.

⁴ Fine, J., Frehling, S., and Starr, A. Experimental Observations on the Effect of Ninety-Five Per Cent Oxygen on the Absorption of Air from the Body Tissues, *J. Thoracic Surg.* **4**: 635, 1935.

CHANGES IN PLASMA VOLUME DUE TO DECOMPRESSION OF THE DISTENDED SMALL INTESTINE

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In a recent experimental study of the factors causing death in cases of uncomplicated acute intestinal obstruction a serious and rapid fall in the volume of circulating plasma was observed¹ This extreme loss of plasma occurred as a result of distention of the obstructed small intestine and continued as long as the distention continued Evidence was obtained that "intravenous plasma in amounts adequate to replace that lost as a result of obstructing and distending the empty small intestine confers a protective influence sufficient to markedly prolong the life of the animal"² This effect was not secured by the use of equal or larger amounts of physiologic solution of sodium chloride

Since distention is responsible for the loss of plasma, decompression should be accompanied by a retardation of the loss or indeed by a gain of plasma volume Experimental data in confirmation of this inference are presented here

METHOD

By a technic described in a preceding publication,¹ dogs under intraperitoneal pentobarbital sodium anesthesia were subjected to a constant intrainestinal pressure of 20 cm of water for some four hours, a period sufficient to produce a substantial fall in plasma volume Decompression was then effected in 3 dogs by applying suction to the cannula in the terminal portion of the ileum continuously for some fifteen hours In these dogs the intestine was subsequently redistended In the remaining group (7 dogs) the distending air current was shut off after four hours, and spontaneous deflation (which occurs readily in the dog) was allowed

From the Surgical Departments of the Beth Israel Hospital and the Harvard Medical School

1 Gendel, S, and Fine, J The Effect of Acute Intestinal Obstruction on the Blood and Plasma Volume, *Ann Surg* **110** 25, 1939

2 Fine, J, and Gendel, S Plasma Transfusion in Experimental Intestinal Obstruction, *Ann Surg*, to be published

to take place. The changes in plasma volume were determined by the technic of Gibson and Evelyn³

RESULTS

A Decompression by Suction—The loss of plasma after four to five hours of distention at a pressure of 20 cm of water in a group of 7 dogs (previously reported on) averaged 35 per cent¹. Maintenance of the same level of intraluminal pressure thereafter was accompanied by a continuing loss of plasma, which reached 55 per cent of the initial volume shortly before death.

In experiment 1 of the present series (see accompanying table, section *A*) the loss of plasma after four hours of distention at a pressure of 20 cm of water equaled 35 per cent, but at the end of a subsequent thirteen hour period of decompression by suction the loss of plasma was 187 per cent of the initial volume, showing a partial recovery of the plasma lost during the period of distention. Experiments 2 and 3 of this group showed similar, though less striking, results. During the period of decompression in these 2 dogs, which lasted some fourteen hours, there was an additional average loss of 59 per cent in plasma volume, which compares favorably with the loss in dogs with no distention and which is in contrast to a 20 per cent additional average loss after a similar interval in dogs with continuous distention (chart 1).

To emphasize the direct relation between loss of plasma and intraintestinal pressure, the initial degree of distention was reestablished for about six hours. The loss of plasma immediately after this second period of distention in 2 of the 3 dogs totaled 50 per cent. The third dog died before a measurement could be made.

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Effect of Decompression on the Plasma Volume and Whole Blood Volume in Acute Intestinal Obstruction

Ex- peri- ment	Weight of Dog, kg	Duration and Procedure	Plasma Volume, Cc	Change in Plasma Volume, %	Total Blood Volume, Cc	Change in			Change in			Comment	
						Volume, Cc	Volume, %	Volume, Cc	Red Cell Volume, Cc	Volume, %	Hemato- crit %		Hema- to- crit %
A Decompression by Suction													
1	9	0	185		866	381							
		1½ hrs distention	315	-35.0	851	536	+28.8				44		+30.1
		13 hrs decompression	394	-18.7	856	462	+17.3				54		+18.5
2	12.2	0	655		1 310	655					50		
		5 hrs distention	507	-18.4	1,438	871	+24.7				61		+18.0
		12 hrs decompression	618	-20.8	1,295	777	+15.6				60		+16.6
3	10.1	0	333	-49.2	925	592	-9.6				64		+23.3
		5 hrs distention	444		752	308					41		
		15 hrs decompression	305	-31.3	663	353	+13.9				54		+24.0
4	13.2	0	285	-35.8	593	303	0				52		+21.1
		6 hrs distention	220	-50.4	478	258	-16.1				54		+24.0
		B Partial Decompression by Spontaneous Deflation											
4	13.2	0	651		1 112	461					41.5		
		4 hrs distention	534	-18.0	1 068	534	+15.8				50.0		+20.4
		15 hrs deflation	570	-12.5	1 561	847	+83.7				59.0		+42.1
5	10.80	0	700		1,111	411					37.0		
		4 hrs distention	434	-38.0	943	509	+23.8				54.0		+15.9
		8 hrs deflation	404	-42.3									
6	15.75	0	359	-48.8	635	276	-32.9				43.5		+17.5
		1 hrs distention	1,075		1,791	716					40.0		
		15 hrs deflation	706	-34.4	1 518	812	+13.4				53.5		+33.7
7	9.00	0	785	-27.0	1,509	724	+1.1				48.0		+20.0
		4 hrs distention	406		706	300					42.5		
		1 hrs deflation	305	-24.0	556	251	-16.4				45.0		+5.8
8	24.75	0	232	-38.0	471	219	-27.0				46.5		+9.4
		8 hrs deflation	302	-25.7	539	237	-21.0				44.0		+3.5
		1 hrs distention	679										
9	1.75	0	587	-13.6									
		1 hrs deflation	593	-31.0									
		8 hrs deflation	607	-2.1									
10	10.10	0	1,060		1 600	1 092					52.0		
		1 hrs distention	1,060		1 600	1 092					52.0		
		1 hrs deflation	1,060		1 600	1 092					52.0		
11	10.10	0	1,060		1 600	1 092					52.0		
		1 hrs distention	1,060		1 600	1 092					52.0		
		1 hrs deflation	1,060		1 600	1 092					52.0		

Intraluminal pressure fell from 20 cm H₂O to 14.5 cm after 15 1/2 hours' deflation

Intraluminal pressure fell from 25 cm H₂O to 11 cm after 7 1/2 hours of spontaneous deflation
loss of 0.9 Kg in weight from time of determination of control blood volume to time of experiment

7 1/4 hours' distention at 20 cm H₂O pressure fell to 10 cm after 12 hours of spontaneous deflation only 2 feet (60 cm) of intestine distended loss of 1.8 Kg from time of determination of control plasma volume to time of experiment

Dog breathed pure oxygen during deflation period to facilitate absorption of nitrogen from intestine pressure of 25 cm H₂O for 4 hours fell to 10 cm after some ten hours of deflation

Loss of 1.45 Kg from time of determination of control plasma volume to time of experiment pressure of 25 cm H₂O for 4 hours fell to 10 cm after 9 hours deflation during which animal breathed pure oxygen to facilitate nitrogen absorption

Pressure of 20 cm H₂O fell to 12 cm after 1 1/4 hours of spontaneous deflation

Pressure of 20 cm H₂O fell to 12 cm after 1 1/4 hours of spontaneous deflation

In some experiments the control plasma volume was determined on the day of the experiment. In some of the others, in which a number of days elapsed between determination of the control plasma volume and the experiment, a loss of weight occurred (see table). In these the control plasma volume may not be reliable, but a comparison of the plasma volume after the initial period of distention and that observed after the period of decompression is valid. In 5 of the 7 experiments (4, 6, 7, 8 and 9) the data show that deflation, even though not complete, effected a return of part of the lost plasma to the circulation (chart 2). In 2 other experiments (5 and 10) plasma continued to

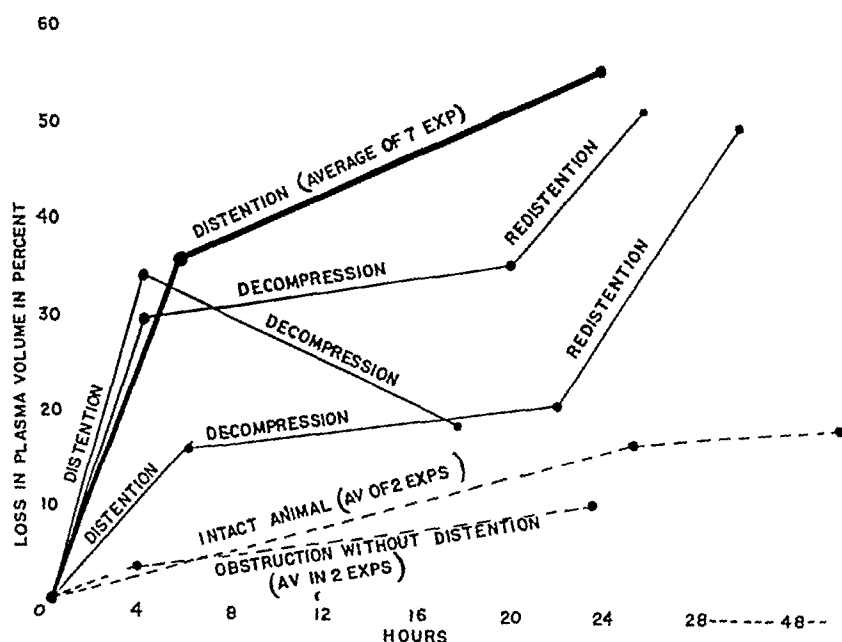


Chart 1—Distention followed by decompression (suction). The heavy black line represents the average percentage loss of plasma in 7 experiments previously reported,¹ in which the entire small intestine of the dog was distended continuously at a pressure of 20 cm of water until death.

Each of the three light solid lines represents the loss of plasma in percentage in single experiments in which continuous distention at the same pressure for several hours was followed by decompression by suction as indicated. Redistention followed, and in 2 a reading was obtained.

The two broken lines represent controls without distention as indicated. All dogs were under continuous pentobarbital sodium anesthesia.

leave the circulation, but at a slower rate than when the intraluminal tension was maintained at the original level.

It is therefore evident that decompression halts the progressive loss of plasma which a sustained level of distending pressure produces and in some instances results in the return of part of the lost plasma to

the blood stream. This process is not always observed to occur immediately after deflation begins. In experiments 7 and 8 the loss continued at least during the first four hours of the deflation period, but substantial return of lost plasma to the circulation was evident in the subsequent measurement of plasma volume.

It will be noted from the table that in 9 of 10 experiments there was a substantial increase in red cell volume concomitant with the decrease in plasma volume during the distention period. This increase may persist, although it tends to disappear as the deflation halts the loss in plasma volume (experiments 1, 2, 3 and 6). As the loss in plasma continues to increase, however, the red cell volume may fall

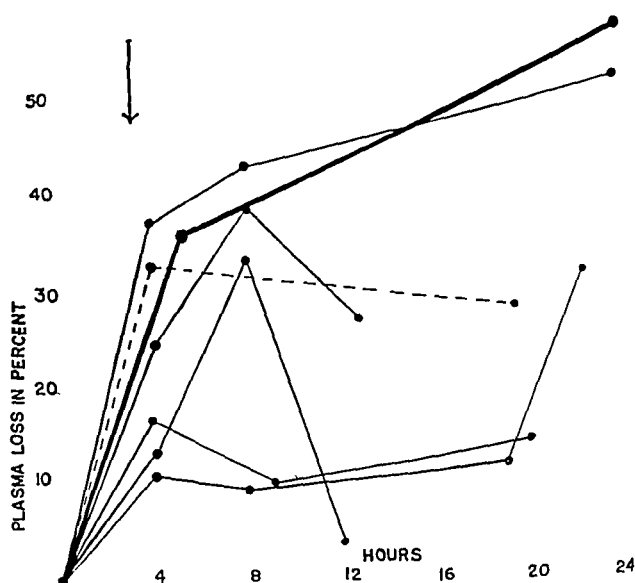


Chart 2—Distention followed by partial decompression (spontaneous deflation). The heavy black line represents the average loss of plasma in percentage in 7 experiments previously reported,¹ in which the entire small intestine was distended continuously at a pressure of 20 cm of water until death occurred. Each of the other solid lines represents the loss of plasma in percentage in single experiment in which the entire small intestine was distended at a pressure of 20 to 25 cm of water for four hours, after which (see arrow) the cannula in the ileum was clamped and partial spontaneous decompression was permitted.

The broken line represents an experiment in which only 2 feet (60.9 cm) of intestine was distended for seven and one-half hours.

below normal (experiments 2, 3 and 5). The rise in the hematocrit reading following distention is therefore partly due to an accession of red cells to the circulating blood. The hematocrit reading must accordingly be regarded as an approximation rather than a faithful index of the extent of the loss of plasma.

Since the rise in the hematocrit reading parallels the extent of the fall in plasma volume induced by distention, a fall in the hematocrit reading toward the initial level may be expected when part of the lost plasma returns to the circulation as a result of decompression. That this occurs is clearly observable in the data on experiments 1, 6 and 7.

The changes in red cell volume are reflected in the figures for total blood volume. The fact that the total blood volume does not fall to the same extent as does the plasma volume is presumably due to mobilization of red cells, perhaps with some plasma, from the spleen and the hemopoietic system. Since the capacity for compensation from such stores is limited, a sharp fall in total blood volume, though not as great as that in plasma volume, appears when the loss of plasma reaches a dangerous level. The variability from one animal to another in the available supply of such supplementary stores of whole blood or red cells may account for the differences in tolerance to plasma loss due to intestinal distention.

COMMENT

It has previously been emphasized that distention is the central problem in acute intestinal obstruction, the only potentially fatal effect we have been able to observe so far from its presence is a marked fall in plasma volume. The experimental procedure utilized to produce this result departs from the natural conditions, however, in that the intestinal pressure was maintained in a closed loop (the entire small intestine) at a constant level until death. When distention develops spontaneously the tension produced by gas when it first enters the intestine is usually not sustained, owing to absorption via the blood stream, relaxation of intestinal muscle tonus, spatial readjustment of adjacent organs and relaxation of the musculature of the abdominal wall. The flexibility of these accommodating mechanisms probably varies from time to time in the same subject and from one species of mammal to another. Thus in the dog an initial intraintestinal pressure of 20 cm of water, if not sustained by a continuous current of air will fall rapidly to a much lower level⁵. There is no reason to doubt that this may also be true in man. Furthermore, in the presence of simple obstruction a patent pylorus will permit decompression by regurgitation of intestinal contents. The rate of loss of plasma in cases of clinical obstruction is therefore likely to change from moment to moment because of the action of many factors with opposing effects, the extent of the fall in plasma volume will become critical only after adjusting mechanisms fail. Hence, in a given person at a given time resistance to the effects of distention will vary in accordance with the state of elasticity of these safety factors and the clinical state of the patient will vary accordingly.

⁵ Unpublished data

Our observations on decompressing the bowel do not support the belief⁶ that death following an apparently adequate decompression of the acutely distended bowel can be due to too sudden a deflation. Such a view may have acquired plausibility from analogous experience with prostatic obstruction of the bladder and (rarely) after excision of large tumors from the abdominal cavity. Evaluation of a therapeutic measure must take account of the stage of the disease at which the measure has been applied. For example, transfusion for exsanguinating hemorrhage is futile, even when given in ample volume, if shock has reached an irreversible stage. Similarly, decompression will fail to reverse the downward course of advanced acute intestinal obstruction, owing to irreversible physiologic changes. According to our data, decompression can halt and even reverse the mechanism of loss of plasma, but the rate of return of the lost plasma to the circulation may be inadequate for the needs of vital areas in danger of collapse from insufficient blood volume. The effectiveness of adequate deflation will depend, therefore, on the extent and duration of the plasma deficiency at the time the deflation is achieved. A fatal result may occur shortly after enterostomy, not because of enterostomy but because the loss of plasma has reached a level from which recovery is not possible without prompt supplying of the enormous deficiency in the volume of circulating plasma.

CONCLUSIONS

1 Decompression of the distended small intestine retards or prevents the progressive and eventually fatal loss of plasma caused by the distention. A return of part or most of the lost plasma to the circulating blood volume can be demonstrated to follow decompression.

2 The rise in the hematocrit reading during distention is only an approximate index of the extent of loss of plasma, because in the earlier stages of the process part of the rise is due to the entrance into the circulating blood of a variable volume of red cells from the hemopoietic system. This accession of red cells to the circulating blood in the earlier stages of loss of plasma will prevent a corresponding loss in total blood volume. However, when the loss of plasma becomes extreme the total blood volume falls markedly below normal. This fall in the total blood volume is never quite as extensive as that of the plasma volume. The hematocrit reading continues to increase as death approaches. In this late stage of the process, therefore, the increase in the hematocrit reading more accurately reflects the extent of the loss of plasma.

3 The recovery of lost plasma achieved by decompression of the distended intestine is accompanied by a fall in the hematocrit reading toward the initial level.

6 Elman, R. The Danger of Sudden Deflation of Acutely Distended Bowel in Late Low Intestinal Obstruction, *Am J Surg* 26: 438, 1934.

GASTRIC SECRETION

I A NEW GASTRIC POUCH WITH A NONLEAKING STOMA AND AN INTACT NERVE SUPPLY, DESCRIPTION OF A TWO STAGE TECHNIC USED ON THE DOG

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The creation of an isolated gastric pouch in experimental animals has contributed more than any other procedure to the present understanding of the physiology of gastric secretion. The extraordinary usefulness of the pouch depends on the fact that it permits quantitative collection of secretion uncontaminated by material from either the esophagus or the duodenum. In no human being, even one with a chance abnormality of the stomach, has a quantitative collection of uncontaminated gastric secretion been obtainable. In patients with pyloric obstruction, for example, gastric secretion is contaminated by saliva, in patients with esophageal obstruction and gastric fistulas the secretion is contaminated by unknown quantities of duodenal contents. In such patients the disease has usually produced nutritional disturbances not conducive to normal secretory function.

The gastric pouch itself, however, has presented drawbacks. Digestion of the abdominal wall by the gastric secretion has prevented maintenance of a sphincter at the outlet of the pouch, and an indwelling catheter has been required for collection of the secretion. Mechanical stimulation has resulted from the presence of the catheter with consequent alteration in the character of the secretion. In spite of constant care, digestion of the abdominal wall has often progressed far enough to cause death of the animal before completion of the experiment.

Up to the present time the major portion of the experimental work has been done with either the Pavlov pouch or the whole stomach pouch. Both types have faults other than digestion of the abdominal

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wall The intactness of the nerve supply of the Pavlov pouch has been questioned in recent years, and removal of the entire stomach from the digestive tract hardly leaves the animal in a normal physiologic state

This paper describes a new gastric pouch with the following advantages The nerve supply is intact, minimal damage is done to digestive function, erosion at the stoma is eliminated, and the necessity of an indwelling catheter is obviated

CONSTRUCTION OF A GASTRIC POUCH (ANTERIOR WALL) IN THE DOG

First Stage—The stomach is exposed through a left paramedian, high abdominal incision (intratracheal ether anesthesia) For convenience of manipulation (1, fig 1) stay sutures are placed in the wall of the stomach at the following four points (A) the lesser curvature of the pyloric antrum, 1 cm below the incisura angularis, (B) the lesser curvature just above the left gastric vessels and posterior to the major trunks of the anterior, or left, vagus nerve¹, (C) the greater curvature 1 cm above the uppermost short gastric vessel, and (D) the greater curvature 1 cm below the point directly opposite the incisura of the lesser curvature

The right gastroepiploic vessels are divided 1 cm above stay suture D The lesser peritoneal cavity is opened into and the omentum is divided along an avascular plane at a right angle to the greater curvature for at least 10 inches (25 cm), allowing separation of the omentum into a gastric and an antral portion

The future pouch is separated from the residual portion of the stomach by incising the wall with a thermal electric cauter. The serosa and muscularis are divided first and allowed to retract, and the vascular submucosa and mucosa are divided secondarily Incision is started at the incisura and carried across the anterior wall of the stomach to a point 1 cm above stay suture D This line of incision is carried on to the posterior gastric wall for a distance of 1.5 cm It is then turned upward at a right angle on the posterior gastric wall, along the greater curvature The incision is kept just far enough from the greater curvature to leave the blood supply from the gastroepiploic vessels intact to the anterior gastric wall, and it stops opposite stay suture C At this point the incision again turns at a right angle, passing to the anterior wall of the body of the stomach, below the true fundus Only that

1 A small incision is made in the gastrohepatic omentum, above the left gastric vessels and below the branch of the left vagus nerve to the porta hepatis (see under "Course and Distribution of the Vagus Nerves") The suture is placed through this incision in the upper portion of the lesser curvature

portion of the gastrosplenic ligament immediately adjacent to the greater curvature need be divided. The main splenic and gastrosplenic vessels are left intact and the spleen is moved together with the anterior gastric wall.

The main trunks of the left vagus nerve are next identified by pulling up on stay sutures *B* and *C*. These nerves overlie the lesser curvature half of the anterior gastric wall (1, fig. 1). Incision is carried with the cautery from the greater curvature toward stay suture *B*, stopping short of the most lateral branch of the vagus nerve.²

Incision is next made along the lesser curvature. The branches of the left gastric artery and vein supplying the anterior wall of the stomach are first identified. A tunnel leading to stay suture *B* is made beneath these vessels and their accompanying sympathetic nerves, along the wall of the lesser curvature. It is usually necessary to divide a small branch from the right gastric artery to the incisura in order to start the tunnel. Vessels and nerves being spared, the lesser curvature is then divided from the incisura to within 0.5 cm. of stay suture *B*. All of the gastric branches of the left vagus nerve will be found anterior to the incision in the lesser curvature.

The final separation of the pouch from the stomach can be accomplished in one of two ways. The small portion of the anterior gastric wall remaining intact beneath the branches of the left vagus nerve may be divided either through the mucosa alone or through the mucosa, the submucosa and part of the muscularis. It is impossible to divide the entire muscularis and serosa without damaging the vagal nerves. If the submucosa, which carries the major blood vessels, is divided, several vessels will need to be clamped and tied individually, since the cautery cannot be used beneath the vagal branches without damaging the nerves. Suturing is made easier, however, if the submucosa is separated.

The pouch is formed by a continuous, inverting (Connell) suture, no. 00 chromic catgut with an atraumatic needle being used (2, fig. 1). The pouch is closed from the top down, making the open end as far from the esophagus as possible. The greater the length of the pouch, the greater the mobility. The rim of the open end of the pouch should be made from the antral edge of the anterior gastric wall. If it is made from the edge of the greater curvature, the vessels and the omentum increase the bulk of the neck of the pouch and make it more difficult to suture in place in the second stage operation. Because of the inequality in length between the greater and the lesser curvature, the infolding suture should be started at the greater curvature, above the gastrosplenic

² The fine branch passing to the true fundus of the stomach lies above the line of incision and is not disturbed in this dissection.

EXPLANATION OF FIGURE 1

Figure 1—1, anterior gastric wall of the dog exposed at operation *A* indicates a stay suture 1 cm below the incisura angularis, *B*, a stay suture on the lesser curvature, above the left gastric vessels, *C*, a stay suture on the greater curvature, above the gastrosplenic vessels, *D*, a stay suture on the greater curvature, opposite the incisura, *LV*, the left vagus trunk, *RV*, the right vagus trunk. The probe lies in the tunnel beneath the left gastric vessels along the line of the incision in the lesser curvature 2, Pouch in the anterior wall, separated from the residual portion of the stomach *P* indicates the pouch, *RS*, the residual portion of the stomach, *ps*, the pouch suture, *ss*, the stomach suture, *A*, a stay suture 1 cm below the incisura angularis, *B*, a stay suture on the lesser curvature, above the left gastric vessels, *C*, a stay suture on the greater curvature, in the gastrosplenic vessels. The upper end of the probe lies in the cardia. In the space between the arrows lies the undivided portion of the anterior gastric wall. The mucosal infolding sutures have been started in the pouch and in the residual portion of the stomach 3, formation of the pouch completed. The residual portion of the stomach has been closed *P* indicates the pouch, *RS*, the residual portion of the stomach, *A*, a stay suture 1 cm below the incisura angularis, *B*, a stay suture on the lesser curvature, above the left gastric vessels, *D*, a stay suture on the greater curvature, opposite the incisura, *LV*, the left vagus nerve, *An*, the antrum 4, anastomosis of the outlet of the pouch to the pyloric antrum *P*, indicates the pouch, *An*, the pyloric antrum, *Du*, the duodenum, *B*, a stay suture on the lesser curvature, above the left gastric vessels, *LV*, the left vagus nerve. The pouch portion of the omentum has been wrapped around the pouch 5, final position of the pouch *P* indicates the pouch, *An*, the antrum, *RS*, the residual portion of the stomach, *Spl*, the spleen, *L*, the liver. At a second operation the outlet of the pouch has been transferred from the pyloric antrum to the left flank. The spleen is swung with the body of the pouch. A suture line closing the antrum remains to be covered with omentum.

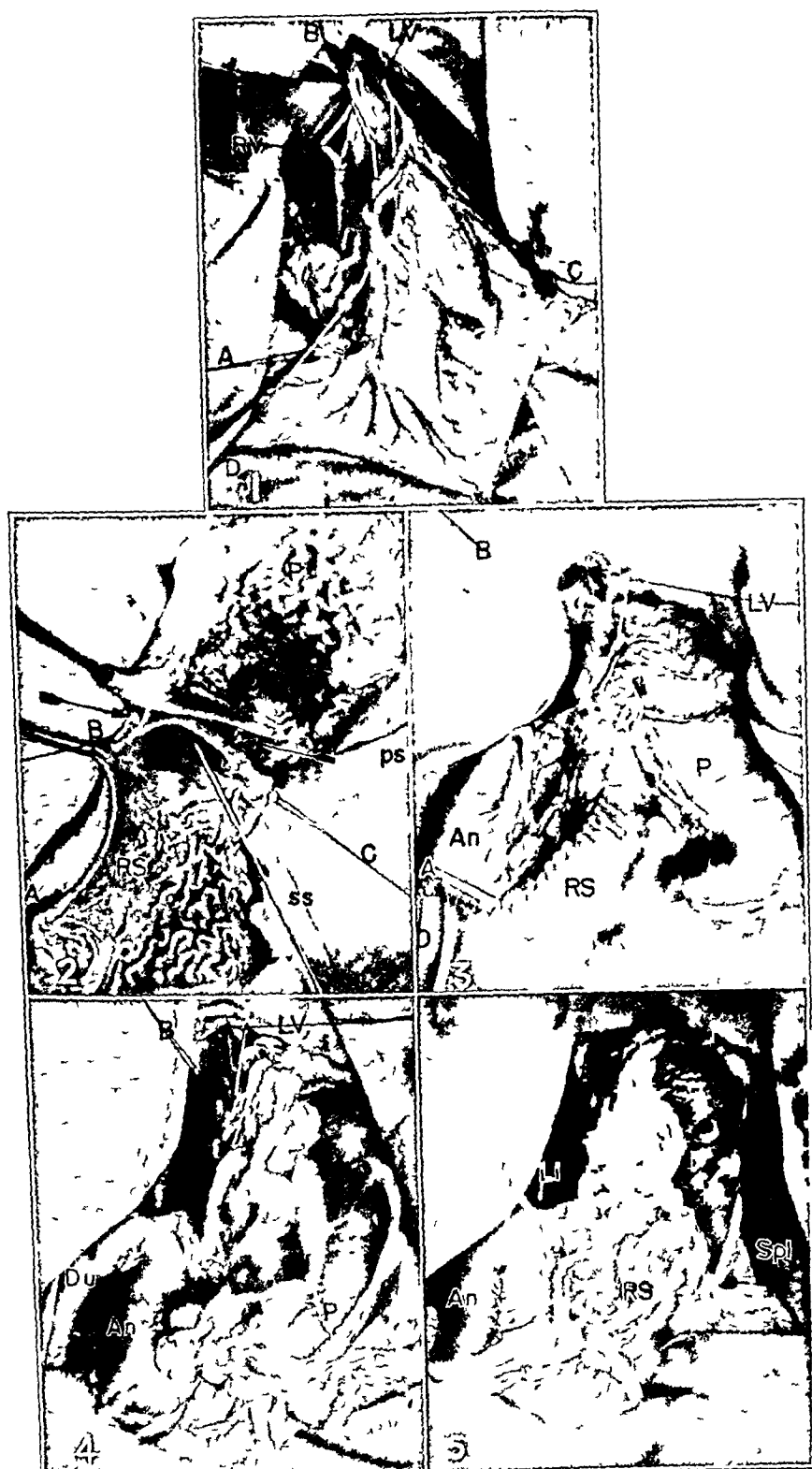


Figure 1

vessels. The first, or inverting, suture includes only the mucosa and the submucosa. The second, running, noninverting, suture approximates the muscularis and the serosa.

The stomach is reconstructed by similar running sutures but is closed completely (3, fig 1). The open end of the pouch is sutured into a 2.5 cm opening made in the anterior wall of the pyloric antrum (4, fig 1).

The antral portion of the omentum is sutured around the stoma and over the gastric suture line. The pouch portion of the omentum is wrapped around the entire pouch and sutured in place. Careful peritonization is important to prevent formation of adhesions between the pouch and the residual portion of the stomach.

Second Stage—An interval of at least three weeks is allowed between the first and the second stage.

A lateral left rectus incision is made. The open end of the pouch is freed from the antrum, a cuff of the antral wall being left attached to the pouch. The cuff should be approximately 1 cm wide and should consist of serosa and muscularis only. The mucosa is divided at the line of previous suture. The hole in the antrum is closed (5, fig 1).

The incision through which the stoma of the pouch is to be brought out is next prepared. It is a stab wound from the skin to the peritoneal cavity, just large enough to accommodate the neck of the pouch. It is made in the costovertebral angle, immediately beneath the left twelfth rib, through the oblique and transversalis muscles, lateral to the quadratus lumborum and semispinalis muscles.³ Care is taken to split, not cut, the muscle bundles, with careful preservation of their different directions.

The pouch is swung posteriorly on its pedicle, and the open end is brought out of the abdominal cavity (5, fig 1). The pouch portion of the omentum and the spleen swing with the pouch. The wall of the pouch neck is sutured to the subcutaneous fascia with divided fine chromic catgut sutures. Care must be taken not to disturb the blood supply to the stoma of the pouch. The cuff of antral wall is sutured loosely out over the skin.

3 Occasionally, if the thoracic cage is proportionately larger than the stomach or if care in suturing the pouch is not taken as described, the pouch will be too short to reach below the twelfth rib without being sutured under tension. The pouch must not be fixed under tension, otherwise it will retract. In this case the open end of the pouch is brought out through the intercostal muscles on the left side, near the spine. The space between either the tenth and eleventh or the eleventh and twelfth ribs may be used. In order to avoid creation of a pneumothorax it is wise to obliterate the lower thoracic space at the first operation by suturing the diaphragm to the chest wall.

A tab of omentum is fastened over the suture line in the antial wall, the left rectus incision is closed

Comment on the Technique—A successful stoma has not been made at the same operation at which the pouch is formed. If the pouch is brought out immediately the sutures are digested away the neck opens along the suture line and the flank wall is eroded by the gastric secretion. Either a defect in the muscle wall develops, damaging the action of the sphincter, or the neck of the pouch promptly retracts into the abdomen. If the neck is well healed before it is brought through the flank, this digestion does not occur, and it is for this reason that the operation has been divided into two stages.

The actual sphincter action depends on the muscles of the gastric wall at the neck of the pouch and also on those of the flank wall. The varied directions of the fibers of the external and internal oblique and transversalis muscles result in an encircling pressure around the neck. The parallel bundles of a single muscle exert only lateral pressure.

The combined sphincter action of the muscles of the stomach and the abdominal wall is ineffective if the neck of the pouch is brought out anteriorly, alongside the sheath of the rectus muscle. The effective sphincter action depends on the fact that the body of the pouch is dependent from the stoma. This is true if the dog is standing or lying on the right side but not if it is lying on the left. The animal, however, learns promptly to lie on the side opposite the wound.

The same two stage procedure can be applied and the stoma in the flank created with the Pavlov pouch, the Heidenhain pouch and other forms of gastric pouch with a sufficiently long body. It was developed while the Pavlov pouch was in use in this laboratory. It cannot, however, be used with pouches having a short body or neck. Hollander and Jemerin⁴ have recently devised one with intact nerve supply but with a neck too short to reach beyond the anterior abdominal wall.

ANATOMIC CONSIDERATIONS

In this effort to improve on previously described experimental gastric pouches made in the dog, the following anatomic facts have been considered.

Distribution of the Gastric Cells—In experimental animals and in man the cells of the mucosa of the pyloric antrum are anatomically different from the glandular cells lining the body of the stomach.⁵ The secretion from the antrum is alkaline or neutral, in contrast to the acid

⁴ Hollander, F., and Jemerin, E. E. Preparation of Stomach Pouch Without Interruption of Vagal Supply, *Proc Soc Exper Biol & Med* **39** 87, 1938.

⁵ Berger, E. H. The Distribution of Parietal Cells in the Stomach. A Histotopographic Study, *Am J Anat* **54** 87, 1934.

secretion from the body of the stomach⁶ Observers have differed as to where the dividing line between the body and the antrum occurs We have been struck by the regularity by which the line can be identified in the dog by gross observation The antral mucosa is relatively pale, firm and flat, the mucosa of the body is more suffused with a purplish tint, softer, thicker and with more prominent rugae

In the dog, not only can the division be recognized grossly, the zone of transition being usually within 1 cm., but it occurs at the incisura angularis along the lesser curvature The incisura is a definite anatomic landmark, and time and damage to tissue are saved by opening the stomach at this point when making either an antral or a body pouch

On the outer surface of the stomach, along the greater curvature, there is no anatomic structure indicating the dividing line between the antral and the body mucosa The line runs, however, at a right angle to the lumen of the stomach, and the point opposite the incisura will not be far from it

There are no similar lines of demarcation between the mucosae of the body, the true fundus and the cardia In the cardia and fundus the mucosa is thinner and smoother, and the folds, so prominent in the body, are largely absent The significance of the cells of the cardia and the fundus in relation to the secretion formed is not yet understood The parietal, or acid-secreting, cells are found in both areas

Blood Supply of the Stomach—The blood supply to the stomach of the dog is essentially similar to that of man The arterial blood is derived from the celiac artery, but the relative size of the branches differs from that of the human stomach in two respects First, the left gastric artery of the dog is proportionately larger, the right gastric branch of the hepatic artery being a relatively small vessel Second, the short gastric branches of the splenic artery in the dog are larger and supply directly about a third of the greater curvature

Course and Distribution of the Vagus Nerves—As a result of experiments conducted in this laboratory with a Pavlov pouch, suspicion arose as to the intactness of the vagal nerve supply Accordingly, an anatomic study of the course and distribution of the vagus nerves was made

In devising his gastric pouch, Pavlov⁷ apparently made no original study of the distribution of the vagus nerves but accepted the description given by Ellenberger and Baum⁸ Reports from independent worker-

6 Gamble, J. L., and McIver, M. A. The Acid-Base Composition of Gastric Secretions, *J. Exper. Med.* 48: 837, 1928, unpublished data from this laboratory

7 Pavlov, I. P. *The Work of the Digestive Glands*, ed. 2, London, C. Griffin & Co., 1910

8 Ellenberger, W. and Baum, H. *Systemische und topographische Anatomie des Hundes* Berlin: Paul Parey, 1891

in more recent years⁹ have shown that the anatomy of the vagus nerves of the dog is not different from that of the human being. While the present study was under way, Jemerin and Hollander also had reason to suspect the intactness of the vagal supply of the Pavlov pouch, and in a recent article¹⁰ they have described the distribution of both vagus nerves to the stomach of the dog. Their findings and those of the present study are in agreement. Jemerin and Hollander, however, limited their investigation to the stomach. The present study has included the course and distribution of the vagus nerves from the hilum of the lungs downward.

Forty-five dogs have been used for this study. The gastric distribution alone of the vagus nerves has been observed in 30 animals as an essential step of the pouch operation. The remaining 15 dogs were killed and dissected in order to make the complete anatomic study. From the first 6 of the latter group the tissues were prepared by the method of Longwell.¹¹ The organs and nerves were excised en bloc and placed in 5 per cent hydrochloric acid in the ice box for twenty-four hours. The nerve fibers being more resistant to the acid than muscle or connective tissue, the method facilitates dissection of the terminal nerve branches. Because the nerve trunks up to the point of penetration of the organ are grossly obvious, the remaining 9 animals were dissected immediately after being killed.

Below the hilum of the lungs the right and left vagus nerves of the dog descend along either side of the esophagus. Between the hilum of the lung and the diaphragm each nerve sends a large anastomotic branch, grossly one-third to one-half the entire nerve, to the vagus nerve on the other side. The branch from the right vagus nerve passes in front of the esophagus on its way to join the left vagus trunk (figs 2 and 3). The branch from the left vagus nerve passes posterior to the esophagus. Each branch joins the trunk of the other side just before the trunk passes through the diaphragm.

⁹ Latarjet, A. Note préliminaire sur l'innervation et l'innervation de l'estomac, *Lyon méd* **130** 166, 1921. McCrea, E. D. The Abdominal Distribution of the Vagus, *J Anat* **59** 18, 1924-1925. Perman, E. Surgical Treatment of Gastric and Duodenal Ulcer, *Acta chir Scandinav* (suppl 38) **77** 1, 1935. Stahnke, E. Experimentelle Untersuchungen zur Frage der neurogenen Entstehung des Ulcus ventriculi, zugleich ein Beitrag zur pathologischen Physiologie der Mageninnervation, *Arch f klin Chir* **132** 1, 1924.

¹⁰ Jemerin, E. E., and Hollander, F. Gastric Vagi in the Dog. Erroneous Assumption of Uninterrupted Vagal Innervation in the Pavlov Pouch, *Proc Soc Exper Biol & Med* **38** 139, 1938.

¹¹ Longwell, S. E. A New Method for Investigation of the Peripheral Nervous System, Muscles and Glands, *Science* **47** 395, 1918.

As a result of rotation of the stomach during fetal life, each vagus trunk shifts in the lower portion of the thorax to a new position in relation to the esophagus. The left vagus nerve acquires an anterior and the right a posterior position. The anastomotic branch from each vagus nerve leaves the trunk in the lateral position but joins the opposite nerve

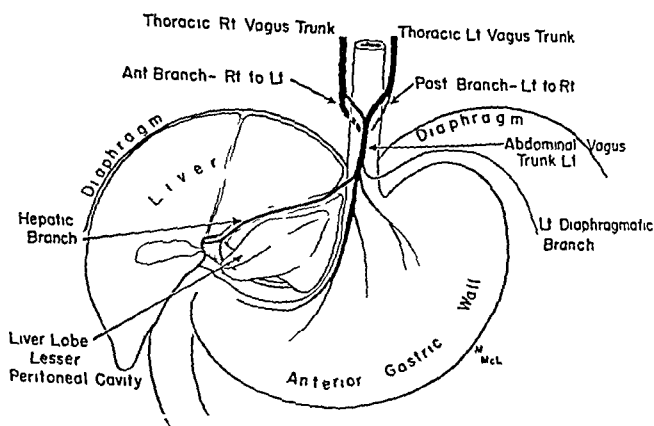


Fig 2—Diagram illustrating the origin and abdominal distribution of the left vagus nerve as observed in dissection of 15 dogs

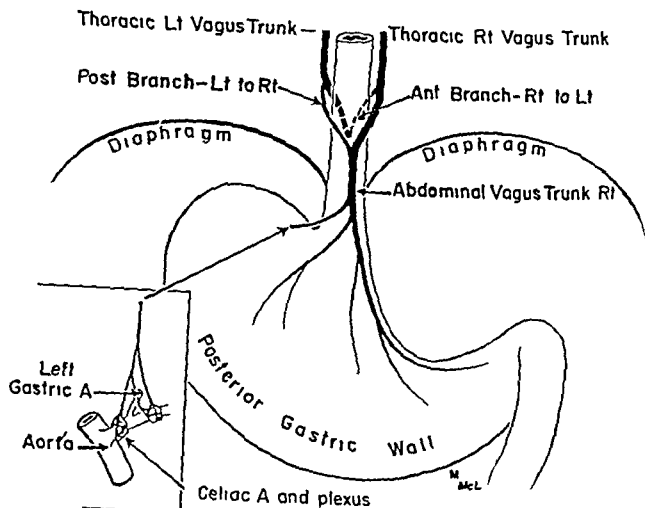


Fig 3—Diagram illustrating the origin and abdominal distribution of the right vagus nerve as observed in dissection of 15 dogs. The insert shows the distribution of the celiac branch

in its new position. The left vagus nerve passes through the diaphragm anterior to the midportion of the esophagus and emerges below the diaphragmatic muscle on the anterior surface of the cardia (fig 2). The right vagus nerve passes through the diaphragm posterior to the esophagus

gus and enters the lesser peritoneal cavity on the posterior surface of the cardia (fig 3). Each nerve lies between the peritoneum and the muscularis.

Each vagus trunk in its passage down the stomach bears a constant relation to the lesser but not to the greater curvature. In the development of the fetal stomach of the dog the lesser curvature is apparently the fixed portion. As the lumen of the stomach increases in size, branches from each vagus nerve pass out from the lesser curvature over the gastric wall toward the greater curvature.

The left vagus nerve supplies the entire anterior wall of the stomach (cardia, fundus, body and antrum), the hepatic plexuses and the left side of the diaphragm (fig 2). As the trunk emerges from the diaphragm a small twig is usually detectable passing to the left side of the diaphragm. The second branch is the hepatic branch. Of medium size and easily recognizable, it arises from the right side of the nerve trunk and runs in the gastrohepatic omentum close to the liver. On reaching the hepatic artery it divides into two terminal branches, one running into the porta hepatis and the other in the opposite direction, toward the aorta, losing its identity in the nerve plexus along the hepatic artery.

The remaining and larger portion of the left nerve trunk passes to the anterior wall of the stomach alone. Including the terminal filament of the trunk, there are usually four gastric branches. The upper two divide soon after leaving the trunk, the uppermost division, a small one, passes to the left to supply the true fundus. In succession the branches pass from the trunk distally as they traverse the body of the stomach, entering the muscularis about one third of the way to the greater curvature. The terminal portion of the trunk pierces the muscular layer near the lesser curvature about 1 cm. beyond the incisura angularis. It is possible that this terminal nerve sends filaments to the pylorus and to the first portion of the duodenum, but filaments have not been found beyond the antrum on gross dissection.

The right (posterior) vagus nerve, like the left, has a threefold distribution (fig 3). The small initial branch goes to the right side of the diaphragm. The second, or celiac, branch is moderately large, is constant and corresponds to the hepatic branch of the left nerve. After leaving the main trunk it divides into three well defined branches. These pass into the dense autonomic plexuses surrounding both the celiac and the lower hepatic arteries. No attempt has been made to discover the final distribution of this vagal branch. Presumably it may be as wide as the sympathetic distribution from the ganglions and plexuses surrounding the celiac artery and its branches.

The gastric branches of the right vagus nerve supply the entire posterior wall of the stomach. The distribution of the fibers is the

mirror image of that of the left vagus nerve to the anterior wall. The trunk and its gastric branches are covered by the visceral peritoneum of the lesser peritoneal cavity.

Variations from the foregoing description of the anatomy of the vagus nerves in the dog are rare in our experience. In approximately half of the dissected animals one or another of the diaphragmatic branches could not be found, presumably they were too small to be recognized macroscopically. In 1 of the 45 animals an anastomotic branch crossed the lesser curvature at the incisura, running from the left to the right vagus nerve.

Until a study by fiber degeneration has been made to determine the distribution of the fibers from the anastomotic branches in the thorax it will have to be assumed that each branch of the thoracic distribution of the vagus nerve sends fibers to the entire abdominal distribution of the opposite nerve. In order to interrupt the vagal supply of the pouch described in this paper it is therefore necessary to sever the left vagus nerve below the anastomotic branch from the right vagus nerve. Likewise, division of either vagus nerve in the neck only partially denervates the entire abdominal distribution of both.

It is also obvious from this study that a gastric pouch made according to the method of Pavlov⁷ has the majority of its vagal fibers cut. Only those running to the base of the pouch are left intact.

Course and Distribution of the Sympathetic Nerves—The sympathetic nerve supply to the stomach of the dog arises from the celiac plexus. The nerve fibers and ganglions form a dense network around the celiac artery and its primary branches. A nerve trunk passes to the stomach with each major artery. Branches from these trunks can be recognized grossly beneath the serosa on the surface of the stomach, alongside each small arterial branch and tributary vein. Each nerve and its accompanying vessels penetrate the muscularis at about the same point. Preservation of direct arterial blood supply to the wall of the stomach insures sympathetic innervation.

CARE OF THE POUCH

A dog with the pouch described in this paper requires peculiar but not arduous care.

The sphincter at the stoma is effective in holding in the gastric secretion from the moment the second stage operation is completed. Periodic emptying of the pouch is necessary to prevent overdistention with consequent forcing of the sphincter. A no. 12 French soft rubber catheter is passed through the stoma, and the gastric secretion is sucked out with a syringe. The frequency of catheterization depends on the experimental conditions. An occasional pouch will hold as

much as 1,000 cc without leaking. Usually, however, it is wise with the average-sized dog to empty the pouch before the contents reach 250 cc.¹²

No complicated dressings, washings or inhaling tubes are needed. Digestion of the abdominal wall is limited to a narrow zone between the gastric mucosa and the skin, the extensive digestion seen with other types of stoma is eliminated.

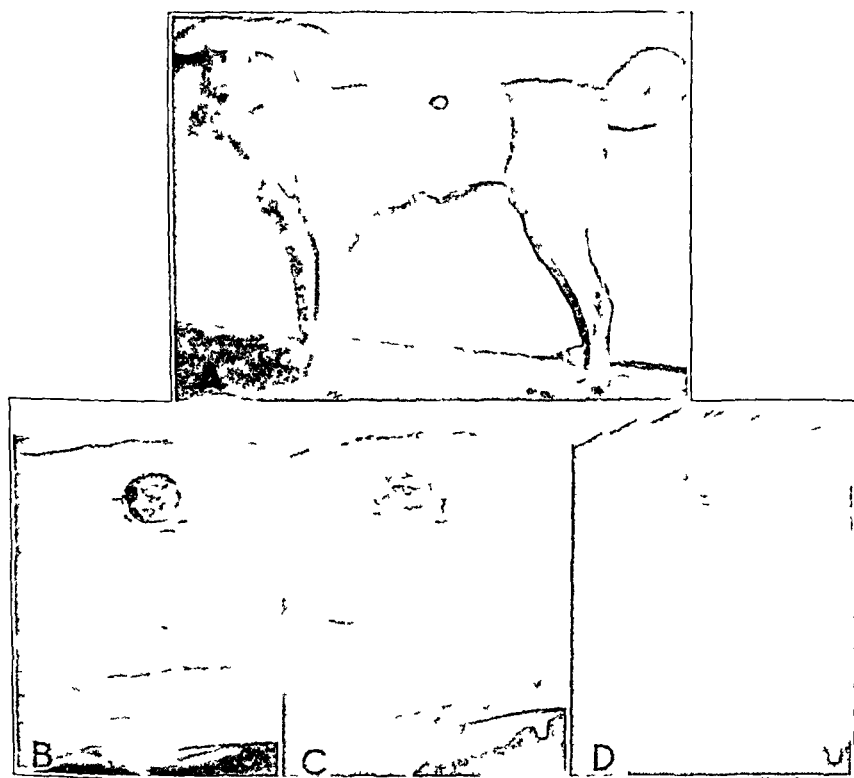


Fig 4—Dog with a pouch of the anterior gastric wall and a stoma in the left flank. *A*, appearance eight days after the second stage operation. *B*, stoma eight days after the second stage operation. Digestion of the cuff of the antral wall has already started. *C*, stoma four weeks after the second stage operation. Digestion of the cuff is nearly complete. *D*, stoma seven months after the second stage operation. Note the absence of digestion of the skin and the regrowth of hair immediately around the stoma.

¹² Some of the dogs will not eat when the pouch is full. Food may lie untouched before the animals. Immediately after the pouch is emptied the food is gobbled up. This observation has also been made on dogs with a Pavlov pouch having the described, improved stoma. Since the vagal supply to the Pavlov pouch is interrupted, it is probable that the afferent fibers carrying the sensation of hunger pass along with the sympathetic autonomic fibers from the celiac plexus.

Operative intervention at the stoma is occasionally required as a result of the changes occurring over a period of months. In the first postoperative days the antral cuff, devoid of an adequate blood supply, swells and becomes glued to the wound with fibrin (figs 4 A and B). The firm ring thus formed prevents retraction of the neck of the pouch until sufficient time elapses for permanent adhesions between the pouch neck and the flank wall to form. Gradually, over a period of two to four weeks, the cuff is digested away (fig 4 C). This digestion is carried out not by gastric juice which has leaked from the pouch but by that secreted from the mucosa exposed at the outlet. With the continued digestion at the very outlet between the mucosa of the pouch neck and the skin, a small fibrous wall results as the permanent stoma (fig 4 D). This fibrous stoma may eventually contract, and it then becomes necessary to cut it in order to pass the catheter without difficulty.

It is the routine in this laboratory to place sodium bicarbonate solution in the pouch after each emptying unless the animal is "on test." It has been found that eventually digestion of the wall of the pouch by the undiluted gastric secretion occurs and ulcers are formed. In the absence of sodium bicarbonate, hemorrhage from ulceration has occurred within periods varying from a week to two months. Several animals have died of perforated ulcers of the pouch following prolonged uninhibited acid peptic digestion. Sodium bicarbonate solution neutralizes the secretion and thereby inactivates the pepsin. Sufficient sodium bicarbonate is added to neutralize the anticipated volume of acid juice. An excess will do no harm.

Care of the animal at night can be reduced to a minimum by feeding once a day, early in the morning. The active phase of gastric secretion lasts for twelve to fifteen hours after the routine laboratory meal. If the dog is fed during the afternoon or evening, provision must be made to empty the pouch during the night.

COMMENT

The pouch made of the anterior gastric wall with its outlet in the flank has the following advantages over previously described gastric pouches.

Intact Nerve Supply—Both the vagal and the sympathetic nerve to the portion of the stomach involved in the pouch remain undivided. The anatomic studies reported in this paper offer confirmatory evidence that the course of the left vagus nerve in the dog is not as described by Pavlov. Vagal fibers are intact to the Pavlov pouch at the base only. From the point of view of vagal innervation, the Pavlov pouch is little better than the Heidenhain

Minimal Denervation Distal to the Pouch—Two areas of the residual portion of the stomach are denervated in making a pouch of the anterior wall. First, the vagal supply from the left nerve to the anterior wall of the antrum is divided. The fibers from the right vagus nerve to the posterior antial wall, however, remain intact, and normal secretory and motor function can be expected from one half of the antrum. Second, the sympathetic nerves to the posterior wall of the body of the stomach, entering together with the vessels of the greater curvature, are severed. The sympathetic nerves to the posterior wall, running with the vessels of the lesser curvature, are not divided. The lesser curvature, at least, of the residual portion of the stomach retains the normal balance between cholinergic and adrenergic activity.

In evaluating experimental observations it may be as important to know what organs have been denervated by the operation as it is to know the innervation of the resulting pouch. Up to the present time, scant attention has been paid to the wide distribution of the vagus nerves in the abdomen. The hepatic and celiac branches of these nerves, for example, might well be severed inadvertently in making a "whole stomach pouch." The resulting loss of the cholinergic, parasympathetic innervation to the liver, pancreas and intestine below the stomach would add to the difficulties of a digestive system already hampered by the loss of the stomach itself.

Quantitative Collection for Unlimited Periods—The described maneuver of bringing the stoma out in the flank permits quantitative collection of secretion for an unlimited number of uninterrupted hours and days. Previous gastric pouches have depended for quantitative collection of secretion on an intubing tube or catheter and a collection bottle slung beneath the animal's abdomen. These have necessitated a constant standing position for the animal, limiting the number of hours for which the experiment could be maintained. Prolonged training was often required. An animal with the pouch described in this paper maintains throughout the period of observation a normal life of standing, walking, lying and sleeping.

Secretion Unaltered by Mechanical Stimulus—Periodic catheterization does not cause the same degree of mechanical stimulation as does catheterization by an intubing tube. The presence of a catheter similar to that described by Pavlov for collection of the secretion stimulates directly the mucosa of the pouch. Such stimulation increases the output of mucin and neutral salt¹³. It is true that the periodic catheterization necessary with the pouch described in this paper must result in some

¹³ Hollander, F, and Cowgill, G. R. Studies in Gastric Secretion. I. Gastric Juice of Constant Acidity, *J. Biol. Chem.* **91** 151, 1931. Data have been obtained also from this laboratory. These are not yet published.

such mechanical stimulation. The gentle passage of a small, soft rubber catheter for the twenty seconds necessary to empty a pouch, however, does not introduce the error associated with the use of a large, constantly indwelling tube.

Long Survival of Experimental Animals—The absence of digestion at the stoma of the pouch allows indefinite survival of the experimental animals. A survival of four months is unusual in an animal with a pouch having its outlet on the anterior abdominal wall. Continued digestion inevitably results in retraction of the neck of the pouch and death from peritonitis.

Easy Care of Animals—The time required by the laboratory technician for the care of a dog with a gastric pouch is shortened to one third by placing of the outlet in the flank. Although catheterization is needed, repeated painstaking dressings with alkaline earths or protein fluids are not.

SUMMARY

An anatomic study of the origin and entire distribution of both vagus nerves in the abdomen of the dog confirms the observation that the vagal supply of the Pavlov type of gastric pouch is not intact.

A gastric pouch in the dog, made from the anterior wall of the body of the stomach, is described. This pouch has the advantage of an intact autonomic nerve supply, both vagal and sympathetic. Minimal neural disturbance to digestive function is created by the formation of the pouch. Only partial denervation, both vagal and sympathetic, is produced in the residual portion of the stomach distal to the pouch and no other organ is denervated.

A new type of stoma for gastric pouches is also described. By a two stage procedure the outlet is made in the flank with the body of the pouch dependent from it. Widespread digestion of the abdominal wall is avoided, and long survival of the animal is made possible. Quantitative collection of secretion can be done over long periods. The mechanical stimulation of secretion is reduced to a minimum by obviating the necessity of indwelling cannulas. The animal is enabled to live a normal life even during periods of observation. The care of the animal is greatly facilitated.

HYPERPLASIAS OF THE MAMMARY GLAND IN THE HUMAN BEING AND IN THE MOUSE

MORPHOLOGIC AND ETIOLOGIC CONTRASTS

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AND

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Evidence accumulating in the last few years has led to wide acceptance of the theory that new growths of mammary tissue are due to abnormal endocrine stimulation. Examination of this evidence shows, however, that it pertains largely to mammary tumors in animals and that the precise nature of the hypothetical glandular dysfunction, even with the much studied mouse cancer, is not known. Especially has little consideration been given the extent to which generalizations derived from animal study may justifiably be applied to the explanation of tumors occurring in man.

Nevertheless, mammary cancer in the mouse continues to afford the best starting point for the study of conditions under which cancer of the breast may develop. Past experiments have already shown the general importance of the ovarian hormone, since it has been demonstrated that the incidence of tumors can be lowered by oophorectomy and raised by administration of estrogenic substances. The search for signs of a peculiar ovarian physiology in mice of the "high tumor strains" might easily give some clue to the type of ovarian dysfunction which should be looked for in women with cancer of the breast.

These studies are, then, an attempt to bring into closer association the problems connected with mammary tumors in the human being and in the mouse. In particular, they are concerned with contrasting the morphologic structure of supposedly precancerous lesions in the mouse and in man and with the possibilities of comparable endocrine disturbances underlying each. They follow a line of research which we believe must be continually returned to as new techniques give opportunities for new types of investigation and new physiologic knowledge requires

From the Memorial Hospital, Breast Service of Dr. Frank E. Adair.

Aided by a grant from the International Cancer Research Foundation and from the Anna Fuller Foundation.

charge from the nipple on the other were investigated on the basis of tissue obtained at operation from parts of the breast outside the abnormal focus for which the surgical procedure was undertaken. The material was thus adapted to show the general structure of the breast in which these respective symptoms occurred. The present material is different in that the sections were from the circumscribed areas which provided the indication for operative intervention. The material, then, should show the more complex characteristic lesions arising respectively in breasts of the two general types.

METHOD

The study of the pathology of chronic mastitis was pursued in the following manner. The occurrence of special pathologic structures or processes, such as cysts, papillomas and fibrosis, was first tabulated for each case. The cases were then sorted into four categories based on general clinical characteristics. The kind of histologic lesions characteristic of each clinical form was thus determined. This step gave evidence that in the group of conditions generally classed as chronic cystic mastitis one is probably dealing with at least two separate entities. The recognition of such a subdivision is naturally essential before any attempt is made to compare spontaneous human with experimental animal mammary lesions.

LESIONS OCCURRING IN CHRONIC CYSTIC MASTITIS

After considerable study it has seemed best to classify the lesions present in the 103 cases under four principal heads, namely: 1 Distortion of the mammary architecture as a result of increase in amount of fibrous tissue or of normally formed acini (adenofibrosis). 2 Proliferation of atypical acini (adenosis). 3 Inflammatory disease of the ducts. 4 Neoplastic disease of the ducts.

1 *Adenofibrosis*—The normal mammary lobule consists of a group of small tubules, branches of a small duct lying within a zone of relatively loose and cellular connective tissue. This tissue causes the lobule to be more or less demarcated from the coarse, acellular connective tissue of the breast as a whole. It has been compared (Moszkowicz¹) with the stroma of the endometrium and a functional similarity suggested, since each tissue surrounds active epithelial elements of the reproductive system and each is affected by the cycles of menstruation and pregnancy.

The size of the lobules and their number unquestionably vary tremendously with the individual person (Dieckmann²). Mammary

1 Moszkowicz, L. Sexualzyklus, Mastopathie und Geschwulstwachstum der Mamma, Arch f klin Chir **144** 138-161, 1927.

2 Dieckmann, H. Ueber die Histologie der Brustdrüse bei gestörtem und ungestörtem Menstruationsablauf, Virchows Arch f path Anat **256** 321-356 1925.

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1 A reexamination of the histology of the diffuse benign lesions commonly grouped under the term "chronic mastitis" to afford a basis for a morphologic comparison with lesions of the mammary gland of the mouse

2 A review of the clinical evidence for ovarian dysfunction in women with "chronic mastitis"

3 An examination of the gross and histologic structure of the mammary glands of two strains of mice (differing in their susceptibility to mammary cancer) at various ages, to compare the spontaneously developing epithelial lesions with those of "chronic mastitis" in women

4 A histologic study of certain of the endocrine organs of the two strains of mice in search for evidence of a specific physiologic difference between the two strains

5 An examination of the gross and histologic structure of the mammary glands of the two strains after the injection of various endocrine substances, again in search of lesions resembling morphologically those present in "chronic mastitis"

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Disagreement as to the actual nature of the pathologic process present in chronic cystic mastitis has existed since the earliest descriptions of the disease In fact, the condition has been at various times regarded as an inflammatory process, a tumor, a congenital anomaly, a form of epithelial hyperplasia and a type of generalized fibrosis Reexamination of the morphologic appearance of the diseased tissue is constantly necessary, as pathologic conceptions change, and is essential at present, when comparisons are being made between this disease and various lesions produced by administration of endocrine substances to animals

MATERIALS

The pathologic material consisted of mammary tissue removed in operation from 103 patients with chronic cystic mastitis Hematoxylin and eosin stains were used for all specimens, and for some of them in stains (sudan III) and connective tissue stains (Masson's trichrome and Van Gieson's) also were employed Besides the pathologic section there were available descriptions of the clinical aspects of the disease in the breast and data on the reproductive and menstrual histories

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changes in relation to the menstrual cycle are probable, but these can scarcely affect the actual number of tubules (Moszkowicz,¹ Diekmann,² Dawson³) It is impossible to establish a "standard breast," and it will lead to error if a diagnosis of pathologic hyperplasia is made simply on the basis of the unusually large size or number of the lobules

The simplest and probably the earliest lesion to be observed in the painful nodular breast without secretion is a loss of the normal architectural relation of the lobule (table 1) This is apparently the result of

TABLE 1—*Clinical Type in Relation to Pathology of Lobule and Acini*

	Group 1 Pain and Nodu- larity	Group 2a Milky Dis- charge	Group 2b Sangu- neous Dis- charge	Group 2c Inde- terminate Dis- charge	Group 3 Pain and Dis- charge	Group 4 No Symp- toms	Total
Number of cases	47	11	9	17	9	10	103
Definition of lobules							
Good	6	2	1	3	0	3	15
Variable	5	5	0	2	3	1	16
Fair	15	1	0	5	3	2	26
Poor	21	3	4	7	3	4	42
Cause of lobular distortion							
No distortion	6	2	1	3	0	3	15
Underdevelopment	6	3	4	6	1	1	21
Fibrosis	13	0	1	1	1	0	16
Fibrosis and cystic dilatation	3	0	0	0	1	1	5
"Diffuse fibroadenoma"	3	0	0	1	0	0	4
Fibrosis and acinar diffusion	4	3	1	0	1	0	9
Diffusion of acini	7	0	1	5	4	3	20
Cystic dilatation only	5	3	0	1	1	2	12
Dilatation of acini							
None	12	1	2	5	1	2	23
Slight	17	6	4	2	1	1	31
Moderate	14	3	3	5	5	4	34
Marked	4	1	0	5	2	3	15
Abnormal acinar proliferation							
None	29	7	7	11	4	7	65
Fibrosis and acinar diffusion	7	3	1	1	1	0	13
Diffusion atypical acini	7	0	1	5	4	3	20
Hypertrophic acini	5	0	0			0	5
Solid acini	2	1	0			3	6
Periacinar inflammation							
None	26	1	3	5	2	6	43
Slight	18	7	4	4	5	3	41
Moderate	3	2	1	6	2	1	15
Marked	0	1	1	2	0	0	4

three principal processes: fibrosis of the specific connective tissue of the lobule; diffusion of the glands beyond the confines of the lobule through the general supporting tissues of the breast; and sometimes cystic changes in the glands within the lobule. A Fibrosis. The occurrence of fibrosis as one of the essential processes in human mammary disease is easily demonstrable. On clinical examination the gland itself appears hard, disklike and sharply defined from the overlying subcutaneous fat. On gross section the breast is white, dense and shining with disappear-

3 Dawson, E. K. Sweat Gland Carcinoma of the Breast. A Monograph. Histological Society, Edinburgh. M. J. 39: 409-438, 1932.

ance of much of the adipose tissue. Surprisingly, in microscopic section even of breasts with a history of recent marked increase in size, epithelial elements are actually rare and insignificant in the mass of new fibrous tissue. Such cases have been noted in a previous publication and by Leriche.⁴

Emphasis has been placed on fibrosis by a considerable list of writers. Marchand,⁵ who was among the first, actually used the term "diffuse fibromatosis." Lexer,⁶ also using this term, noted that the interglandular tissue at times has an almost sclerotic quality and stated the belief that the cystic dilatation is due to compression of the ducts. Berthels⁷ likewise maintained that the increase in connective tissue is the primary process and that as a result of the ingrowth of interlobular tissue into the lobules the acini are separated and strangulated. Secondary to this fibrosis there develop, according to this writer, secretion stasis, round cell infiltration and regressive and progressive epithelial changes. Many other writers have placed great importance on the connective tissue aspects of the disease (Dietrich,⁸ Todyo,⁹ Kuckens,¹⁰ Consten¹¹). Still others, though not regarding the connective tissue change as the sole primary one, have accorded it more or less importance (Theile,¹² Cheate and Cutler,¹³ Semb,¹⁴ Greenough and Hartwell¹⁵) and have agreed that it is associated with the new formation of epithelial elements.

4 Leriche, R. Hypertrophie mammaire douloureuse, fletie par castration, *Lyon chir* **20** 653-655, 1923.

5 Marchand. Diffuse Fibromatose der Mamma, *Munchen med Wchschr* **63** 396, 1916.

6 Lexer, K. Fibromatose der Mamma, *Beitr z klin Chir* **88** 662-670, 1914.

7 Berthels, A. Ueber die Mastitis chronica (cystica) und ihren Uebergang in Carcinom, *Deutsche Ztschr f Chir* **124** 9-45, 1913.

8 Dietrich, A. Ruckbildungsvorgange, Fibromatose und Krebs, *Deutsche Ztschr f Chir* **195** 145-156, 1926.

9 Todyo, T. Ueber die cystische Entartung der Brustdruse, *Arch f klin Chir* **104** 440-454, 1924.

10 Kuckens, H. Ueber die Fibrosis mammae und die mit ihr zusammenhangenden Geschwulstbildungen, *Beitr z path Anat u z allg Path* **80** 40-115, 1928.

11 Consten, A. Ueber die diffuse Fibromatose der Brustdruse beim Manne, *Deutsche Ztschr f Chir* **167** 264-281, 1921.

12 Theile, P. Zur Kenntnis der fibroepithelialen Veranderungen der Brustdruse unter Berucksichtigung des klinischen Verhaltens, *Arch f klin Chir* **28** 261-302, 1908-1909.

13 Cheate, G. L., and Cutler, M. Tumors of the Breast, London, Edward Arnold & Co., 1931.

14 Semb, C. Pathologico-Anatomical and Clinical Investigations of Fibroadenomatosis Cystica Mammae and Its Relation to Other Pathological Conditions in Mamma, Especially Cancer, *Acta chir Scandinav (supp 10)* **64** 1-484, 1928.

15 Greenough, R. B., and Hartwell, H. F. Chronic Cystic Mastitis. A Study of Thirty Cases, *J M Research* **9** 416-444 1903.

In this series, simple fibrosis or connective tissue proliferation in association with glands was evident in the majority of the cases in which pain and nodularity were present (table 1). It occurred in several forms. In one the entire supporting tissue of the breast was reduced to dense acellular hyaline connective tissue with islands of almost lost acini in clusters without any of the usual "mantle" connective tissue about them (fig 1). In some areas, not dissimilar in appearance to those observed in myomas of the uterus, hyaline degeneration was noted. In such cases the entire supporting connective tissue of the breast had apparently been involved, with replacement not only of the parenchymatous but also of the adipose tissue of the breast. In another type some evidence of lobulation remained, but the individual acini were separated and entirely surrounded by dense connective tissue replacing the normal loose areolar tissue of the lobule (fig 2). Finally, in rarer cases, laminated concentric rings of connective tissue surrounded the ducts and the acini and gave a fibroadenomatous structure. Sometimes this merely demarcated single lobules from the surrounding tissue, in other instances the areas of diffuse fibrous and adenomatous change gradually became nonencapsulated fibroadenomas. Evidence of inflammation was notably absent in these cases.

b *Fibrosis with Diffusion of Glands* In a smaller percentage of cases the lobulation was found to be lost as a result of diffusion of relatively normal-appearing glands through the supporting tissue of the breast. Arrangement of glands in lobular form was not present, but single tubules, often somewhat dilated, were scattered at more or less regular intervals throughout the microscopic fields (fig 3). That proliferation of connective tissue accompanies this development of acini is almost a certainty but is hard to prove except when the diffuse acini are surrounded by a definite zone of typical periacinar connective tissue. Such a nonencapsulated fibroadenoma is probably analogous with the diffuse adenomyoma of the uterine walls, with its glands and accompanying endometrial stroma.

The normal lobular architecture may also be disturbed by dilatation of the acini to form small cystic structures. This process is usually accompanied by some degree of fibrosis or diffusion of the acini beyond the confines of the lobule and appears to be simply a part of the general condition described as adenofibrosis.

2 *Proliferation of Abnormal Acini*—A good deal of controversy, possibly somewhat futile, has existed over the distinction between a duct and an acinus or alveolus. Certain writers prefer to avoid the issue by reserving the term alveolus or acinus for the secreting unit.



Fig 1—Diffuse fibrosis of the breast with absence of lobules in a married woman aged 41 with marked nodularity and premenstrual mammary pain. The patient had had one miscarriage. The menses were normal.



Fig 2—Intralobular fibrosis in a childless married woman aged 39 with postmenstrual pain and marked nodularity. The menses were normal. The tissue was obtained on the eleventh day of the cycle.

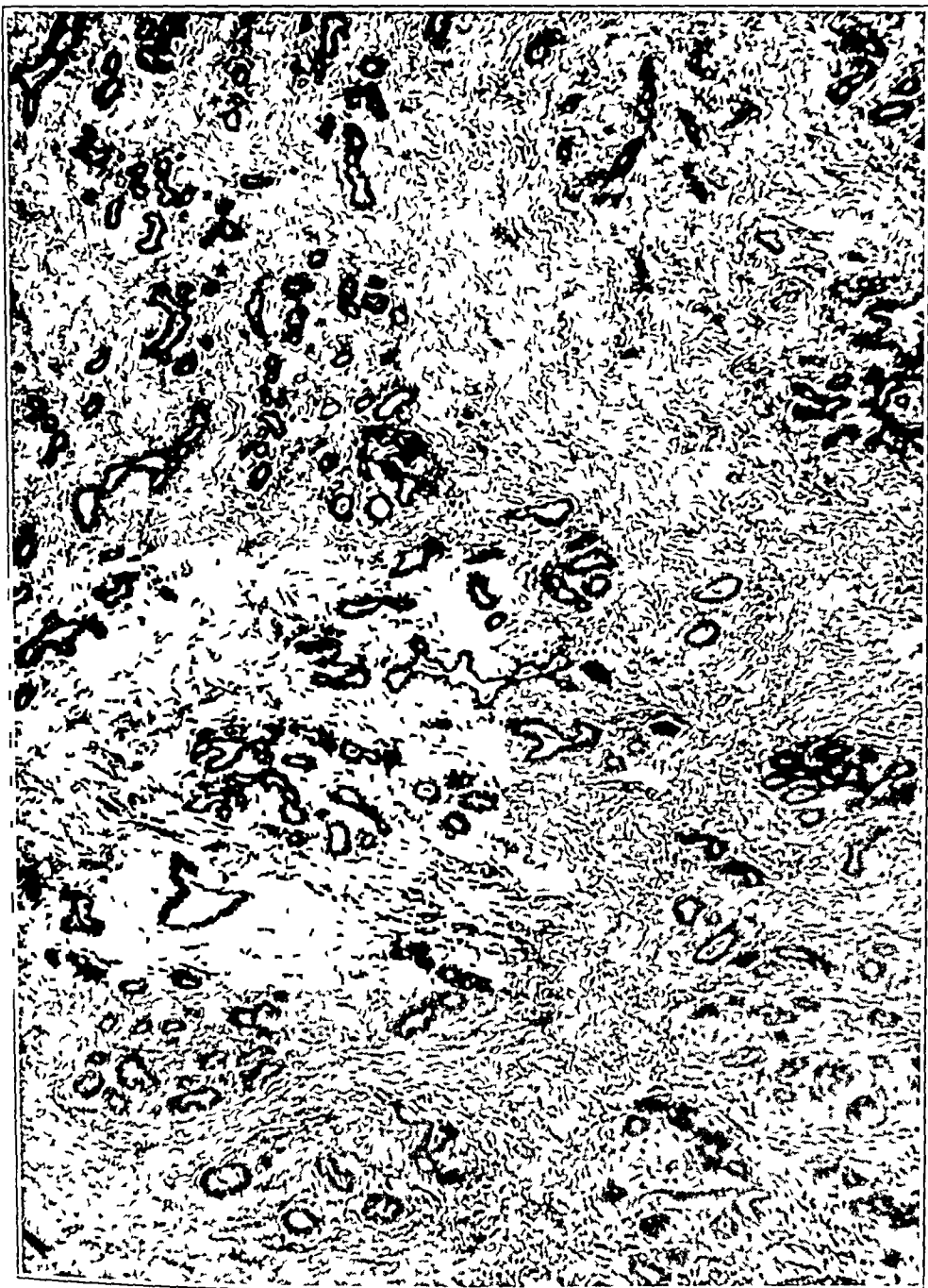


Fig 3—Loss of lobulation by diffusion of acini in a married woman aged 38 with premenstrual pain in the breast and nodularity of the outer quadrant. The patient had had children. The menses were normal. The tissue was obtained on the fifth day of the cycle.

of the lactating gland and referring to the smaller units in the gland of the nonpregnant female as ductules (Dawson³)

The matter is not without importance. In the lower animals, in which the distinction can more easily be made, the growth of the duct system has been ascribed, on the basis of certain experiments, to one glandular principle and that of the acini to another (Turner and Frank¹⁶). This theory of contrasting physiologic origin has been carried over to human pathology and made the basis of a theory of origin of different types of mammary disease, one based on the estrogenic and the other on the corpus luteum hormone (Lewis and Geschickter¹⁷). A second point of importance is that human mammary cancer is now regarded as usually ductal in origin and only exceptionally acinar. The ability to distinguish, therefore, between ducts and acini in the human breast is of immediate theoretic and ultimate practical importance.

The literature indicates a decided confusion in the identification by various writers of these different structures. From perusal of their work and from observation of this series of cases, it appears to us doubtful that arbitrary distinctions between the terminal ducts and the acini are possible. A sharp difference in their physiologic control likewise seems improbable, and to distinguish them after a pathologic process has set in, quite impossible. When the terms are used in the following pages, the word acinus is employed to refer to the tubules of smallest caliber, especially when grouped in a lobular arrangement, whereas statements on the behavior of the ducts are based as a rule on observations made on only the medium and larger ducts.

Proliferation of abnormal acini was not a common finding in this series of cases and when it occurred exhibited several forms. In one group the tubules were dilated and lined by several tiers of cuboidal cells. In another group many of the acini were enlarged and seemed to be proliferating. In a third group there was apparently an increase in the number of very small tubules, often so closely packed as to leave only a few fibers of connective tissue between them and frequently taking the form of solid cell groups (fig 4). Areas were encountered in some places where distorted cords of cells and acini extended irregularly beyond what should have been the margin of the lobule. The latter mentioned type, occurring rarely in this series of cases, resembled somewhat a miniature carcinoma.

16 Turner, C. W., and Frank, A. H. The Relation Between the Estrogen Producing Hormone and a Corpus Luteum Extract on the Growth of the Mammary Gland, *Science* **73**: 295, 1931.

17 Lewis, D., and Geschickter, C. F. Ovarian Hormones in Relation to Chronic Cystic Mastitis, *Am. J. Surg.* **24**: 280-304, 1934.

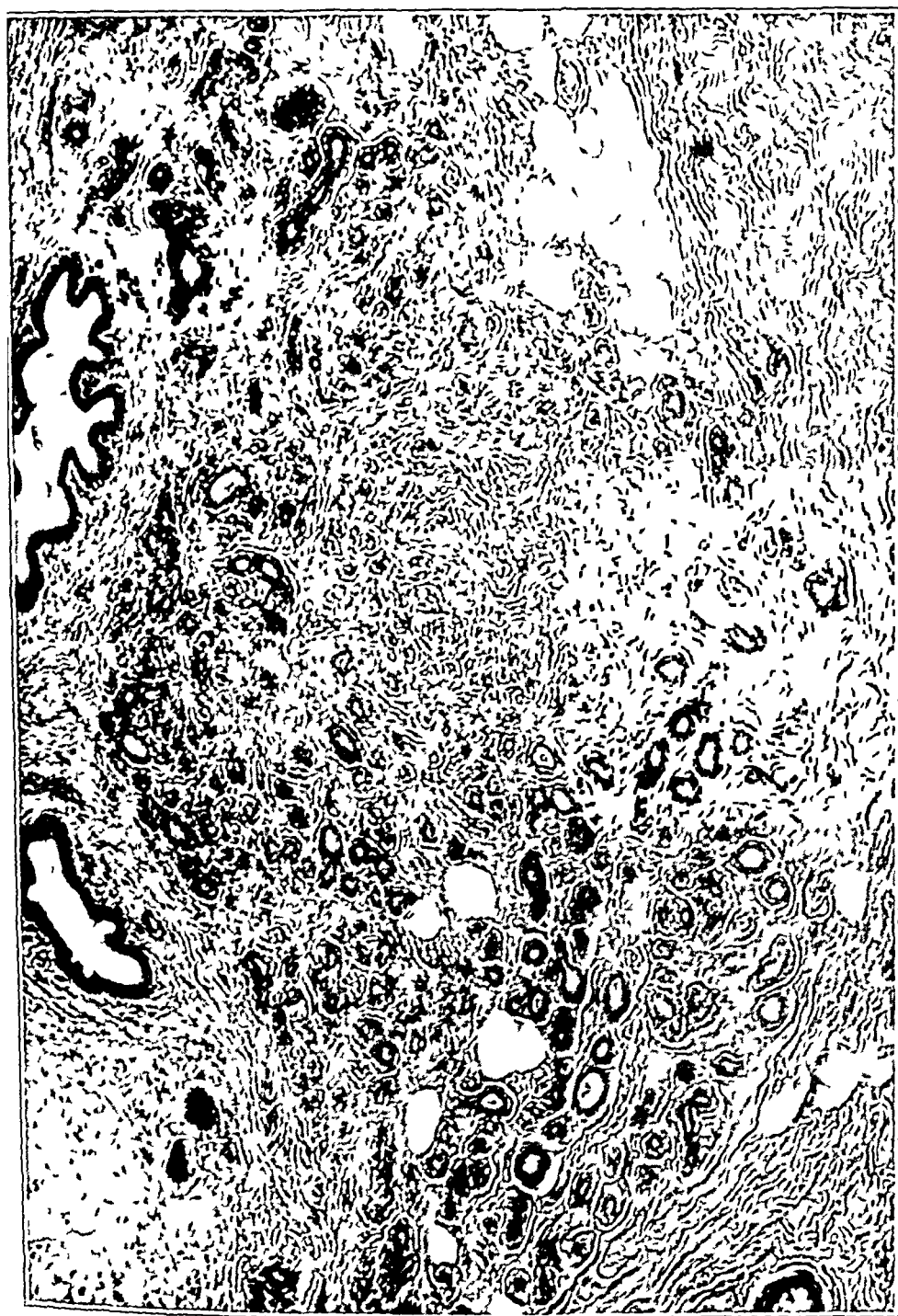


Fig 4—Proliferation of the acini in lobular formation in a married woman aged 48 without mammary symptoms or nodularity except for the lump removed. The patient had had children. The menses were normal.

Morphologically considered, this atypical acinar proliferation bears a close relation to the common diffuse process just described as adenofibrosis. It is perhaps simply a subdivision of that condition, arising locally as relatively intense proliferation or even regeneration of acini. On the other hand, examples of it were found also in sections from patients with secretion from the nipple and even with breasts apparently normal except for the lump removed.

This relatively uncommon acinar proliferation may be of considerable importance. It is the form of human mammary lesion which, as will be pointed out later, resembles most closely the type of abnormal proliferation developing in the glands of mice susceptible to mammary carcinoma.

3 Disease of the Ducts—In the simplest form of disease of the larger mammary ducts, the chief pathologic feature is not neoplasia but inflammation. The lining of the duct is normal. The caliber is perhaps somewhat increased, but the connective tissue beneath the duct is infiltrated with lymphocytes and sometimes plasma cells, scattered diffusely or occurring in small collections (fig 5). The inflammation is most marked about the large and medium-sized ducts, but it occasionally extends into the lobules, which are edematous and infiltrated with round cells. This inflammation is apparently due to absorption of degenerating secretion and duct contents. It is found in the breast with a discharging nipple and subareolar thickening and never in the type with diffuse, fibrous nodularity and premenstrual pain.

In some of the cases studied the ducts contained cells with large pale-staining cytoplasmic bodies and round, distinct nuclei (fig 6). In others, similar cells lined the ducts or were noted in various stages of separation from them. The ducts with these swollen, desquamating cells showed in a few instances evidence of proliferation of their normal lining cells (fig 7). This condition, apparently similar to the "desquamative hyperplasia" of Cheate and Cutler,¹³ was encountered chiefly in cases of duct stasis. Whether these cells represent simply ductal epithelium in some stage of function or degeneration or are fat-containing endothelial leukocytes is not certain.

4 Abnormal Proliferation of Ducts—Hyperplastic and neoplastic disease of the larger ducts may develop with one of two types of epithelium.

a "Sweat Gland" Epithelium The cells of the acidophilic or "sweat gland" epithelium are cylindric, several times as large as those of normal ducts or acini, with a round vesicular nucleus and nucleolus and abundant eosinophilic, faintly granular cytoplasm. This epithelium was found in the form of various structures, namely as a single tubule within a cluster of otherwise normally staining ducts and acini or as



Fig 5—Periductal inflammation in a married woman aged 36 with a yellowish discharge from the nipples. The patient had had children. She was menstruating for two and one-half days at intervals of twenty-one days. The tissue was obtained on the eighth day of the cycle.



Fig 6—Cellular contents of the ducts in a married woman aged 66 without pain or nodularity but with a turbid, serous discharge from the left nipple. The patient had had children. She had passed the menopause.



Fig 7—"Desquamative hyperplasia" in a married woman aged 42 with neither pain nor a discharge from the nipple, operated on for a circumscribed nodule arising in the breasts with moderate bilateral diffuse nodularity. The patient had had children. The menses were normal.



Fig 8—Hyperplasia of the lining of the ducts in a married woman aged 40 complaining neither of pain nor secretion but simply of an isolated nodule in an otherwise normal breast. The patient had had children. The menses were regular. The tissue was obtained on the fourteenth day of the cycle.



Fig 9—Small papillomas and "arcades" in the ducts of a married woman aged 62 with no symptoms or signs except a serosanguineous discharge from the left breast. The patient had had children. She had been seven years in the menopause.

group of tubules in a normally constructed lobule or as the lining of all the members of a cluster of cysts. Cysts composed of "pale" epithelium have many projections into their cavities, which, however, have sometimes more the appearance of broken septums than of true papillae.

This "pale" epithelium is a characteristic finding in cases of human chronic cystic mastitis. It has been accorded a varying degree of importance since its first description by von Saar¹⁸. Krompecher's¹⁹ work claiming that the "sweat gland" cysts are the result of a congenital anomaly and that they give rise to carcinoma represents one extreme view. Dawson,³ at the other extreme, maintained that they are directly derived from normal epithelium and have no relation to sweat glands or to carcinoma formation. She concluded that their peculiar staining reaction indicates a previous proliferation followed by a form of degeneration. Our studies do not indicate the association of this epithelium with any special type of chronic mastitis.

b Neoplastic Proliferation of Duct Lining. More definite evidence of proliferation was found in the ducts composed of normally staining cells. Perhaps the simplest structure noted was the formation of clusters of dilated ducts with relatively low, inactive-appearing epithelium. In slightly larger ducts small cells were found heaped up so that the epithelium consisted of several layers of cells (fig 8). In others the lining of the duct was much more complex, "arcades" and small papillomas being present (fig 9). In a few cases smaller ducts were completely occluded by cells, while in the larger ones complex papillomas were present. These different structures appear to be members of a progressive series of proliferative forms of the same basic nature.

SUMMARY

It may be reiterated that for a claim to be made that "chronic cystic mastitis" has been reproduced experimentally in animals, at least a fair proportion of the morphologic forms of the human disease must be demonstrable. These may now be summarized as follows:

1 Adenofibrosis

a Fibrosis of the lobule

b Diffuse proliferation of normally constructed acini with connective tissue

18 von Saar, G. E. Ueber Cystadenoma mammae und Mastitis chronica cystica, Arch f klin Chir 84 223-279, 1907.

19 Krompecher, E. Zur Histogenese und Morphologie der Cystenmamma (Maladie kystique Reclus, Cystadenoma Schimmelbusch, Mastitis chronica cystica König) des intrakanalikulären Kystadenoms und der Kystadenokarzinome der Hidrokystadenocarcinoma der Brustdrüse Beitr z path Anat u z allg Path 62 403-472, 1916.

- 2 Abnormal acinar proliferation
 - a Multiplication of layers of cells lining the acini
 - b Multiplication of small acini in lobular arrangement
 - c Loss of lobulation by diffusion of acini
 - d Appearance of solid tubules and coalescing cell masses
- 3 Non-neoplastic disease of the ducts
 - a Dilatation of the ducts with secretion in the lumens
 - b Inflammation of periductal tissues
 - c Abnormal function or degeneration of epithelium
- 4 Abnormal proliferation of duct cells
 - a Sweat gland epithelium
 - b Neoplastic proliferation of the ducts
 - i Groups of cystic ducts
 - ii Reduplication of the cells lining the ducts
 - iii Formation of "arcades"
 - iv Occlusion of ducts by cells
 - v Papillomas

EVIDENCE FOR SEPARATION OF TWO DISTINCT ENTITIES
FROM THE GROUP OF CONDITIONS CALLED
CHRONIC CYSTIC MASTITIS

A review of the literature on chronic cystic mastitis shows an almost complete absence of work correlating clinical aspects with specific histologic characteristics. Such a correlation is of obvious importance. From a purely practical standpoint it is of value to know the probable microscopic structure underlying given clinical manifestations. Furthermore, classification is simplified by consideration of a few general characteristics, such as the clinical signs and the gross appearance of the tissue. Dependence should not be placed wholly on the complex patterns of histologic structure.

It was formerly assumed that the various morphologic forms observed in the diffuse benign processes in the breast represented various stages in the life history of a single process. More recently there has been a tendency to segregate certain separate types of the disease and to develop the belief that they represent distinct entities. Cheate and Cutler¹³ have distinguished between "mazoplasia," a condition characterized in part by hyperplasia of the pericanalicular and periacinar tissue, and "cystiferous desquamative epithelial hyperplasia," a more active process with hyperplasia of the epithelial cells of cysts and formation of arcades and papillomas. Lewis and Geschickter¹⁷ have somewhat less definitely separated "adenosis" from "cystosis," and Semb,¹⁴ "fibroadenomatosis simplex" from "fibroadenomatosis cystica."

The 103 cases in the present study were classified on the basis of certain general characteristics into the following four groups, at first without reference to their histologic characteristics

1 Cases of pain in the breast, usually premenstrual, and diffuse increased density or nodularity of the breasts with no secretion from the nipple (47 cases)

2 Cases of discharge from the nipple, usually with slight acyclic pain and little nodularity except for the distended ducts about the nipple (37 cases) This group was subdivided into (a) cases of typical milky

TABLE 2—*Clinical Type in Relation to Pathologic Change in Ducts*

Number of cases	Group 1 Pain and Nodu- larity 47	Group 2a Milky Dis- charge 11	Group 2b Sangu- neous Dis- charge 9	Group 2c Inde- terminate Dis- charge 17	Group 3 Pain and Dis- charge 9	Group 4 No Symp- toms 10	Total 103
Inflammation of duct							
None	37	1	5	2	2	4	51
Slight	6	5	3	5	6	3	28
Moderate	4	1	1	7	2	2	18
Marked		4	0	3	1	1	9
Dilatation of duct							
None	13	0	1	1	0	0	15
Slight	25	1	2	2	4	2	36
Moderate	6	5	6	8	2	7	34
Marked	3	5	0	6	3	1	18
Pale epithelium							
Absent	36	9	6	14	6	5	76
Small areas	5	0	0	2	0	1	8
Papillary cysts	6	2	3	1	3	4	19
Abnormal proliferation of duct epithelium							
None	33	4	4	4	6	4	55
Clusters of cystic ducts	2	1					3
Reduplication of lining epithe- lium	8	6	1	6		5	26
"Arcades"		1	1				2
Solid epithelial masses	1		1	4			6
Small papillomas	3	1			3		7
Large papillomas	0		4	4		3	11

discharge, (b) cases of serosanguineous discharge, and (c) cases of a mixed or unclassifiable type of discharge

3 Cases in which the characteristics of both groups were present, that is to say, premenstrual pain, diffuse nodularity and discharge from the nipple (9 cases)

4 Cases in which the characteristics of both group 1 and group 2 were absent, that is to say, in which there was neither pain nor discharge from the nipple, the only sign being a symptomless lump in an otherwise normal breast (10 cases)

Tables 1 and 2 show that with certain clinical characteristics a pre dominance of one type of histologic lesion may be expected

Group 1—On clinical examination the painful nodular breast is often enlarged and the gland itself is sharply demarcated from the softer

overlying fat. Frequently the edge of the mammary tissue is so well defined as to have a clearly saucer-like outline. Usually the induration is more marked in the outer quadrant and the central ducts are not evident on palpation. There is no secretion from the nipple.

Reports on the histologic appearance of this condition are ambiguous and contradictory. Sebening²⁰ has described for it a state of chronic proliferation of the lobules, with their failure to take part in what he conceived to be the normal changes of the menstrual cycle. Cotte and Pallot²¹ described a thickening of the periacinar basement membrane. Rosenburg²² ascribed the premenstrual pain to epithelial proliferation, Moszkowicz¹ ascribed it to hyperplasia of the glandular fields, and Cheatle and Cutler¹³ ascribed it to distention of the ducts with desquamation of the epithelial cells. The extreme examples, such as the one described by Leriche⁴ as generalized fibrosis, perhaps afford better material for discovering the essentials of this pathologic process than do the mild conditions, for in the latter the characteristic tissue changes may not be developed enough to be classifiable.

In the present series of cases the most consistent abnormality was distortion of the lobule, usually by fibrosis (figs 1 and 2), sometimes by a coordinated growth of fibrous tissue and acini (fig 3). Slight dilatation of the acini was often present, but the ducts were relatively normal. Evidences of inflammation were practically absent. Abnormal proliferation of the acinar or ductal epithelium occurred at times but was a relative rarity.

The disease apparently takes various forms. At one extreme there is some localization of the lesion, producing a structure transitional to the fibroadenoma. In other examples the process is diffuse, and one notes the separation and diffusion of the acini by strands of coarse connective tissue. That the general supporting tissue of the breast partakes in this process is shown by the disappearance of adipose tissue, evident even on gross examination of some specimens. When the breast is markedly affected, microscopic sections show little but the acellular, sometimes even hyaline, connective tissue with small islands of lost acini. New acini may also be found in some cases in which one observes diffusely growing connective tissue and acini without evidence of lobule formation.

20 Sebening, W. Zur Physiologie und Pathologie der Brustdrüse. *Arch f klin Chir* **134** 464-485, 1925.

21 Cotte, G., and Pallot, G. Etude histologique et experimentale de certaines hyperplasies mammaires premenstruelles douloureuses, *Gynec et obst* **33** 113-133 1936.

22 Rosenburg, A. Ueber menstruelle, durch das Corpus luteum bedingte Mammaveränderungen, *Frankfurt Ztschr f Path* **27** 466, 1922.

The process is at times complicated by atypical and what may well be later developing epithelial proliferation (fig 4). That these changes are secondary is suggested by their inconstant presence and the fact that they are unevenly distributed or only focally present. The frequency of these less typical changes is, of course, exaggerated in such a series as this, in which the tissue removed represented more or less circumscribed nodules.

The basic process in the painful nodular breast is therefore fibrosis or at most *adenofibrosis*. The clinically evident increase in the density of the breast is due to the new fibrous tissue and the premenstrual pain to engorgement and edema of the lobules within the nonyielding fibrous connective tissue about them. The histologic structure and the clinical symptoms are closely analogous to those associated with uterine adenomyosis. The proper term to describe the condition pathologically is fibroadenomatosis, as suggested by Semb,¹⁴ or, more simply, *adenofibrosis*.

Group 2a—The gross characteristics in this group are distinct from those of the preceding one. The induration is more central (it may even be entirely retroareolar) and has never the characteristic localization in the outer quadrants. When the breast is cut grossly, the tissue has not the smooth, shining, pure white appearance of that in the previous group but may be honeycombed with cavities which ooze a milky fluid or tubular casts of pasty material.

In this general group the basic histologic change is dilatation of the larger ducts and the filling of these with amorphous material or colostrum-like cells (figs 6 and 7). About the ducts there appears a zone of lymphocytic infiltration of variable extent (fig 5). Occasionally necrosis takes place and local abscesses develop. The lobular structure is sometimes normal, but often the lobules are large and numerous. In some sections, on the other hand, especially those taken near the areola, the lobules may be small or insignificant. Often there is edema of the lobules with considerable lymphoid infiltration suggesting an ascent of infection along the ducts to this point. Signs of secretion within the cells of the lobules may be present, but such secretion is often unexpectedly slight.

In this series, atypical epithelial proliferation was not a consistent finding in the cases of milky discharge from the nipple. When it occurred, it usually took the form of reduplication of the lining cells (fig 8) of the large ducts. Rarely, more complex structures, such as small papillomas, were present.

Group 2b—In the typical case of this group there was bleeding from the nipple, often with no other clinical abnormalities. On gross section a dilated duct might be seen, with perhaps a definite papilloma.

This group is characterized histologically by various types of epithelial hyperplasia, especially of the ducts. There may be reduplication of the epithelial lining, formation of pseudofollicles or "arcades" (fig 9) or complete filling of the ducts with solid masses of cells or by complex papillomas. The absence of these structures in the histologic sections in some cases of bleeding is perhaps to be explained by the failure of either the surgeon or the pathologist to select the right area for section.

Group 2c—The group with mixed types of discharge, variously designated as "watery," "serous" or "amber colored," apparently included representatives of each of the two preceding groups.

Group 3—The group with both cyclic pain and discharge from the nipple was also heterogeneous. Histologic study showed both the acinar and the ductal type of structure.

Group 4—The clinical feature of this group was the absence of all mammary changes or symptoms except for an isolated lump. As might be expected, in several of these cases the condition was simply a localized adenomatous process affecting both lobules and ducts and exhibiting a very complex structure.

CONCLUSIONS

- 1 There are at least two, and possibly more, separate entities which have been called chronic cystic mastitis.

- 2 The first type is characterized clinically by a diffuse nodularity, more marked in the outer quadrant, and by premenstrual pain. On gross section an increase in fibrous tissue is often evident. The basic histologic lesion is fibrosis or adenofibrosis involving the interstitial fat as well as the periacinar tissue. The ducts are relatively little affected. Dilatation of the glands and various evidences of epithelial hyperplasia are important and frequent complications but do not characterize the disease. The condition is analogous to adenomyosis of the uterus and should be termed adenofibrosis.

- 3 A second definite type of mammary disease is characterized by a discharge from the nipples, often associated with palpable dilatation of the ducts near the areola. The basic histologic observations are edema of the lobules with perhaps some evidence of secretion in the cells, dilatation of the ducts, periductal inflammation and possibly some hyperplasia of the lining of the ducts. Depending on the conditions present, the disease should be termed nonpuerperal lactation, periductal inflammation or duct hyperplasia.

- 4 A third type is perhaps to be recognized in lesions arising more or less locally, such as a single papilloma in the larger ducts or the isolated nodules of Schimmelbusch's disease.

5 The exact character of the individual lesions of chronic cystic mastitis and the association of certain of these to form separate entities must be recognized before any comparisons can be made with the lesions artificially produced by administration of endocrine substances to the lower animals

TABLE 3—*Clinical Type of Mammary Disease in Relation to Reproductive and Menstrual History and to Pelvic Lesions*

	Group 1 Pain and Nodu- larity	Group 2a Milky Dis- charge	Group 2b Sangui- neous Dis- charge	Group 2c Inde- terminate Dis- charge	Group 3 Pain and Dis- charge	Group 4 No Sym- ptoms	Total
Number of cases	47	11	9	17	9	10	103
Average age	35.0	36.3	48.4	41.1	33.8	42.2	37.3
Reproductive history							
Single	15	0	0	0	1	3	19
Married, sterile	11	0	2	0	1	3	17
Married, miscarriages only	4	1	0	0	0	0	5
Married, children	17	10	7	17	7	4	62
Menstrual characteristics							
Normal cycle	34	5	4	9	6	7	65
Short cycle	5	0	0	2	2	2	11
Long cycle	2	6	2	1	0	0	11
Irregular cycle	3	0	0	0	0	0	3
Hysterectomy	3	0	0	1	1	0	5
Menopause	0	0	3	3	0	1	7
Normal duration	35	9	5	11	6	6	72
Short duration	9	2	1	2	2	3	19
Pelvic examination							
Normal fundus	14	3	5	6	3	3	34
Retroversion, 2 to 3 degrees	9	5	1	7	3	4	29
Previous hysterectomy	3	0	0	1	1	0	5
Other pathologic change of fundus	2	0	1	0	0	0	3
Normal adnexa	22	7	7	13	4	7	60
Diseased adnexa	6	1	0	1	3	0	11
Normal cervix	14	2	5	6	2	2	37
Diseased cervix	14	6	2	8	5	2	37
No examination	19	3	2	3	2	3	32
Type of mammary pain							
Cyclic pain	36	0	0	0	9		45
Other pain	11	3	2	2	0		18
No pain	0	8	7	15	0	10	40
Breast secretion							
Secretion unilateral	0	2	6	15	4	0	27
Secretion bilateral	0	9	3	2	5	0	19
No secretion	47	0	0	0	0	10	57
Breast consistence							
Nodularity diffuse	10	5	1	4	1	2	23
Nodularity, outer quadrant	30	3	0	0	4	0	37
Nodularity central	0	2	3	5	1	0	11
Normal consistency	3	1	5	8	1	8	26
No note on consistency	4	0	0	0	2	0	6

II ENDOCRINE DYSFUNCTION IN WOMEN WITH CHRONIC CYSTIC MASTITIS

The clinical evidence for an endocrine dysfunction in a series of 261 cases of chronic mastitis and the results of certain hormone assays on a part of this group were recently published in detail. The investigation indicated that a considerable percentage of patients with chronic

mastitis suffered from abnormal menstrual periods. At the same time, studies on the excretion of estrogenic and gonadotropic hormones, with the limitations of technic then available, failed to show any significant deviations from the normal. In the present paper it is proposed only to report the clinical evidence of ovarian disorder obtained from the study of 103 cases on which the histologic work was based and in particular to correlate the functional history with the pathologic types.

In table 3 are set forth data on the endocrine factors which may have affected the breasts of the patients. Two points are of special importance, reproductive history and menstrual disturbances.

REPRODUCTIVE HISTORY

Of the patients with painful nodular breasts, only 17 of 47 (36.2 per cent) had borne children, while of the patients with discharge from the nipple 41 of 46 (89.2 per cent) had children. All of the patients with a simple milky discharge had been pregnant. This contrast was evident also in the cases of the previous report and is clinical corroboration of the claim that two distinct entities are being dealt with.

MENSTRUAL DISTURBANCES

Disturbances of the menses affect a minority of patients with chronic mastitis but are more frequent than in normal women. A decrease in the amount and duration of the menstrual flow in the cases of painful nodular breast (adenofibrosis) has been noted by several previous writers²³ and was again evident in about a fifth of the present series. The consistency with which this rather uncommon anomaly of menstruation has been reported in this type of case appears to establish its association with the disease.

23 (a) Cooper, A. P. *Illustrations of the Diseases of the Breast*, London, Longmans, Rees & Co., 1829, chap. 9, p. 76. (b) Copland, J. *A Dictionary of Practical Medicine*, New York, Harper & Bros., 1859, pt. 5, pp. 929 and 936. (c) Cutler, M. *The Causes of "Painful Breasts" and Treatment by Means of Ovarian Residue*, J. A. M. A. **96**: 1201-1205 (April 11) 1931. (d) Miller, C. J. *Pelvic Lesions as a Contributing Factor in Chronic Cystic Mastitis*, Am. J. Obst. & Gynec. **10**: 375-379, 1925. (e) Rosenthal, M. *Ueber Neuralgien der Mamma und neuralgische Brustdrüsenknoten*, Wien med. Presse **14**: 25-28, 1873. (f) Taylor, H. C., Jr. *Gynecological Aspects of the Etiology and Treatment of Chronic Mastitis*, Surg., Gynec. & Obst. **57**: 627-636, 1933; *The Relation of Chronic Mastitis to Certain Hormones of the Ovary and Pituitary and to Coincident Gynecological Lesions*, *ibid.* **62**: 129-148 and 562-584, 1936. (g) Velpeau, A. A. L. M. *A Treatise on the Diseases of the Breast and Mammary Region*, translated by M. Henry, London, Sydenham Society, 1856. (h) Whitehouse, B. *Mastopathia and Chronic Mastitis*, Surg., Gynec. & Obst. **58**: 278-285, 1934. (i) Witthauer, K. *Ueber Neuralgia mammae*, Beitr. z. Geburtsh. u. Gynäk. 1902, pp. 42-50.

In 6 of 11 cases of milklike secretion (group 2a) a delay in menstruation was noted, which is also corroborative of previous reports. This delay in menstruation may be accepted as a characteristic of many patients with anomalous secretion from the breasts.

It is noteworthy that only 4 of the patients of this series had passed the menopause. Of these, 3 suffered from bleeding nipple and 1 exhibited an isolated lump in an otherwise normal breast. The papillomas of the ducts and the circumscribed complex adenomatous proliferations are to be regarded as nearly independent neoplasms, while the more diffuse processes, occurring before the menopause, are to a greater extent dependent on ovarian function.

Finally, reference should be made to organic abnormalities of the pelvic organs, particularly multiple follicle cysts of the ovaries, reported in a previous paper (Taylor^{23f}). While the significance of these in relation to the origin of chronic mastitis is not obvious, the ovarian findings assume more importance in the light of those to be described for mice susceptible to mammary carcinoma.

III SPONTANEOUS LESIONS RESEMBLING CHRONIC MASTITIS IN TWO STRAINS OF INBRED MICE

In the previous section of this paper, the histologic structure of human chronic mastitis was analyzed and certain characteristics selected as probably representing basic processes. Two types of this disease, adenofibrosis and hyperplasia of the ducts, were described, and reasons were given for believing that they are separate entities. Henceforth these terms will be used in describing precise histologic lesions, the term chronic mastitis being reserved for both groups, especially when referred to in a clinical sense.

For the experimental study of chronic cystic mastitis the mouse has certain great advantages. Spontaneous abnormal proliferation of the mammary epithelium occurs frequently, and the degree to which it develops varies with some hereditary factor. In these respects the conditions are more like those in the human being than are those known to occur in any other animal. One of the first steps must be a consideration of the histologic character of the spontaneously occurring lesions in this animal, particularly its similarity to that of spontaneous mammary lesions developing in women.

The relative incidence of mammary carcinoma in mice has been studied in great detail, at first in reference to some hereditary factor present in certain inbred strains of mice but also with regard to the life histories of reproductive function and to the effects of administration of endocrine principles. Histologic investigation of the precancerous lesions of the mouse's breast to supply material in any way comparable with that collected from the many pathologic studies of human disease is largely lacking.

Such a study of the benign proliferation of the mouse mammary gland is an essential step in establishing the value of work done on mouse mammary cancer for explaining carcinogenesis in the human breast. It is also necessary for the present investigation to establish the normal before proceeding to the effects of injection of various endocrine substances.

METHODS

Two strains of mice were selected, differing greatly in their susceptibility to spontaneous mammary carcinoma. The strain with the low incidence of tumor was the C57 strain of black mice, that with the high incidence, the Little dilute brown strain (dba). Considerable literature exists on the incidence of cancer in these strains (Murray,²⁴ Little,²⁵ Bagg and Jackson²⁶).

Neither the animals used for controls nor those to be described later, which received injections of endocrine substances, were ever mated. Vaginal smears were made daily, and the animals were killed as far as possible during estrus in order to avoid the complication of considering histologic changes based on the cycle alone.

Histologic examination was restricted to the five glands from the left side of the animal. Ten to twenty sections were obtained from each and stained with a routine hematoxylin-eosin technic.

The mammary glands of the right side were mounted grossly according to the technic described by Turner and Gardner.²⁷ By this method the layer of subcutaneous fat and fascia containing the ramifications of the mammary gland are stripped from the muscles below and the skin above, stained with hematoxylin and mounted in balsam on a slide beneath a cover glass.

These gross mounts appear to us almost essential. The mouse mammary gland is spread out over a wide area but lies almost in a single plane. Microscopic sections cutting across this plane show only a few ducts and acini and give a very poor conception of the gland as a whole. Differentiation between ducts and dilated acini seems almost impossible without the aid of these special preparations.

NORMAL MAMMARY GLAND OF A MOUSE OF THE "LOW TUMOR STRAIN"

The mammary glands of 15 animals of the C57 strain varying in age from 3 to 14½ months were examined (table 4).

The gross preparations (figs 10, 11 and 12) showed the mammary tissue to be made up of a relatively simple duct system with from three

24 Murray, W. S. The Breeding Behaviour of the Dilute Brown Stock of Mice (Little dba), *Am J Cancer* **20** 573-593, 1934.

25 Little, C. C. The Constitutional Factor in the Incidence of Mammary Tumors, *Am J Cancer* **27** 551-555, 1936.

26 Bagg, H. J., and Jackson, J. The Value of a "Functional Test" in Selecting Material for a Genetic Study of Mammary Tumors in Mice and Rats, *Am J Cancer* **30** 539-548, 1937.

27 Turner, C. W., and Gardner, W. U. The Relation of the Anterior Pituitary Hormones to the Development and Secretion of the Mammary Gland, *Research Bulletin 158, University of Missouri College of Agriculture, Agricultural Experiment Station, 1931*.

to four series of branches. The ducts were all relatively slender, straight or curved. The ends were rounded, with sometimes two to three short terminal branches. These were often slightly club shaped and represented everything that might be considered an acinus. Side branches along the course of the ducts were, as a rule, absent.

Microscopic sections (fig 13) showed the relative infrequency of these ducts. Often five or six cross sections of tubules were all that could be found in a given preparation. The larger ducts were lined by

TABLE 4—*Age of Animals for Studies of Normal Breast*

"Low Cancer Strain" (C57)		"High Cancer Strain" (dba)	
Mouse No	Age in Days	Mouse No	Age in Days
6A	86	12	90
7A	86	13	90
51	105	63A	100
73	135	42	107
30	168	36	168
33	168	31	168
75	168	01	178
76	168	03	178
23B	176	43	210
50A	176	53	230
29	236	04	230
50B	236	71	232
74	346	54	292
46	346	70	344
19	438	69	344
		50B	360
		49B	360
		48	366
		33	414
		35	414
		44	417
		46B	417
		63B	42
		60B	412
		64	412

one or two layers of small, dark cells with little secretion in the cell bodies or in the lumens. The smaller ducts or acini were insignificant, collapsed bodies of tightly packed nuclei with little evidence of cytoplasm. The connective tissue was delicate and scant about both the larger and the smaller ducts.

There was little difference in the complexity of the duct system of the older and that of the younger animals (figs 10 to 13). In 4 mice more or less pronounced dilatation of the ducts occurred, and in 1 peculiar clubbed ends were present. These were the only cysts, in contradistinction to dilatation of the ducts, that were encountered in the entire study of both treated and untreated animals.

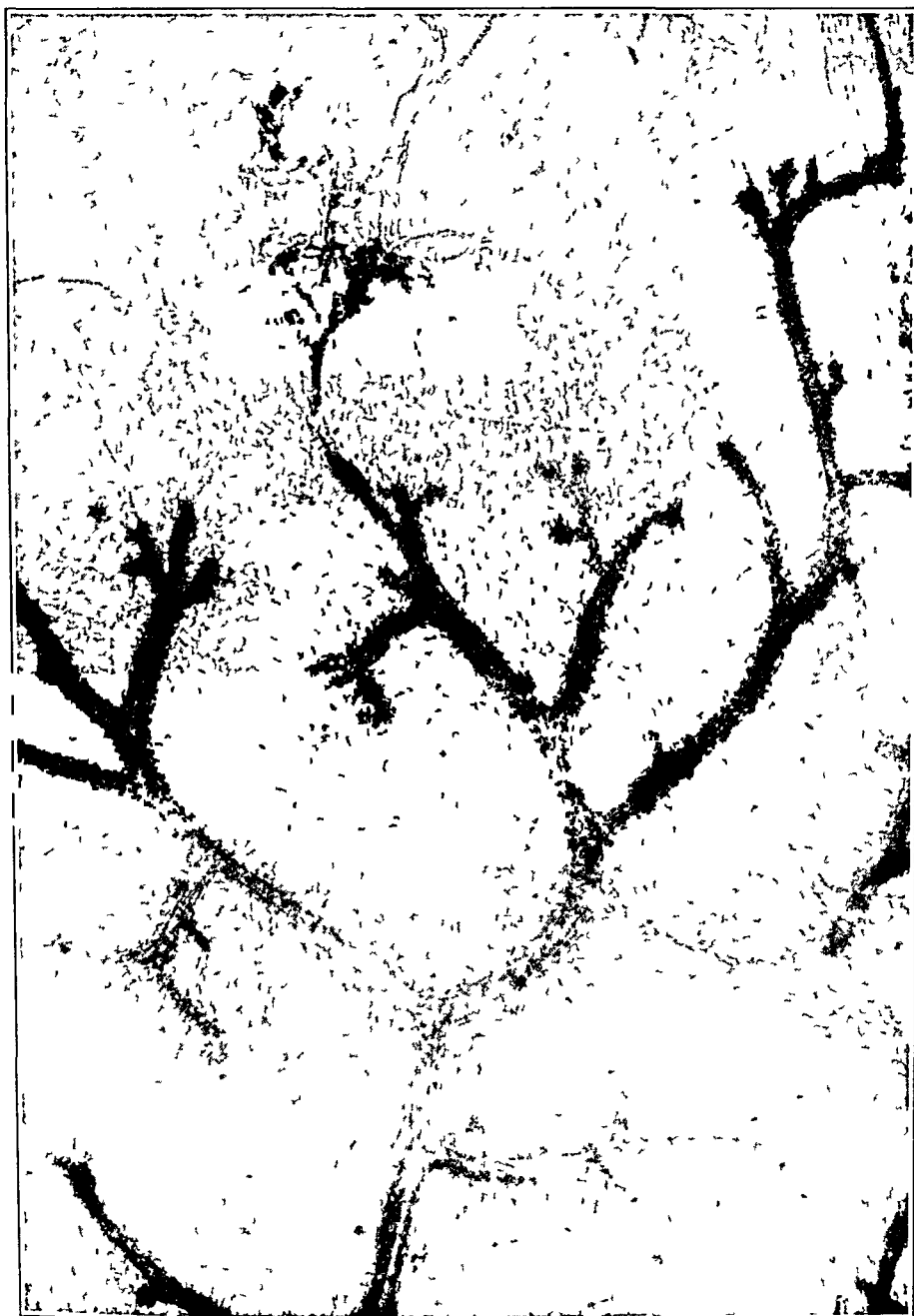


Fig 10—Simple duct system in the mammary gland of mouse of the "low tumor strain" at the age of 86 days. Gross preparation.



Fig 11—Simple duct system with absence of acini in a mouse of the "low tumor strain" at age of 168 days. Gross preparation

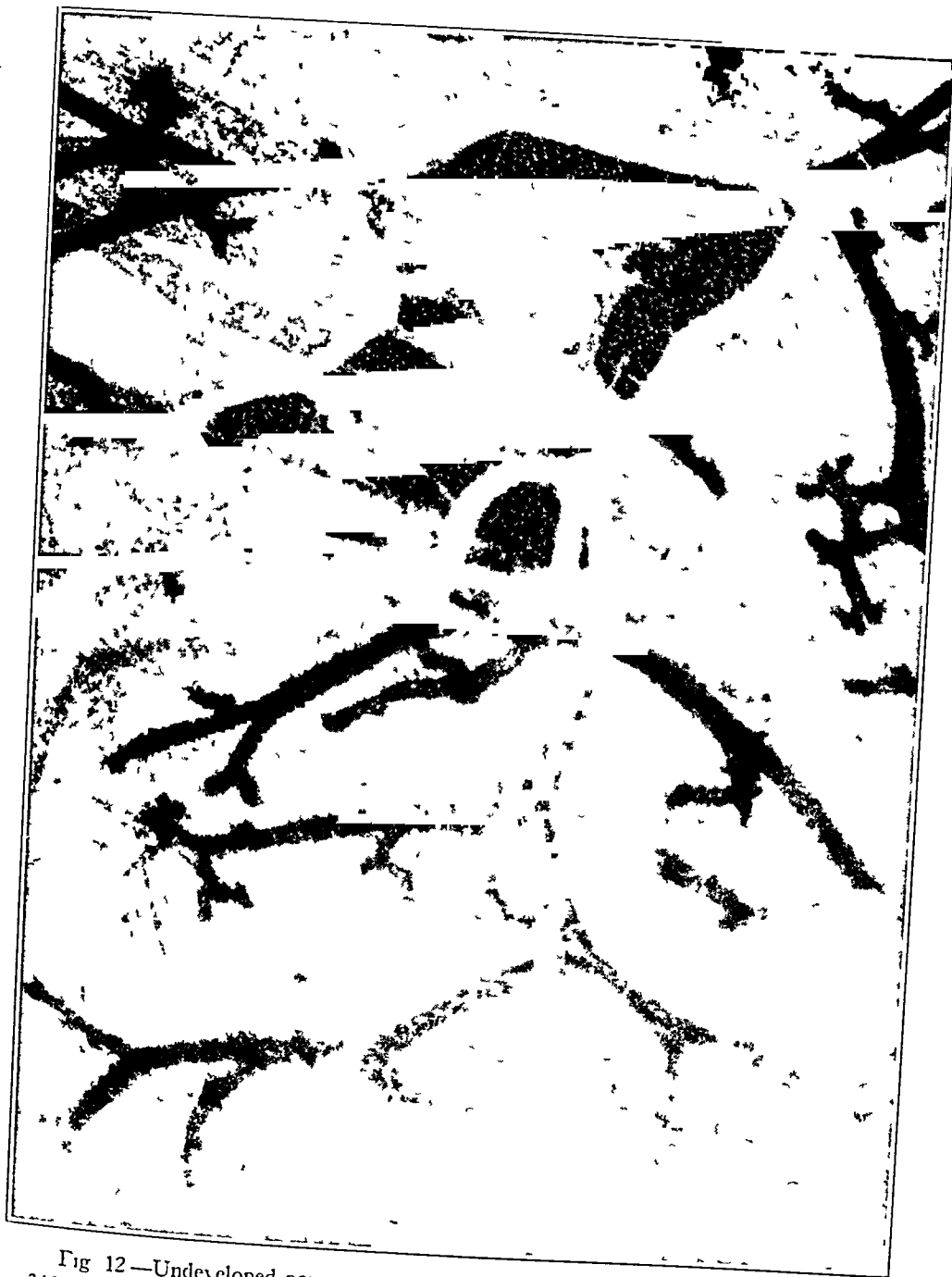


Fig 12—Undeveloped acini in a mouse of the "low tumor strain" at the age of 346 days. Gross preparation



Fig 13—Large ducts with undeveloped acini in a mouse of 'the 'low tumor strain' at the age of 346 days. Microscopic preparation.

NORMAL MAMMARY GLAND OF A MOUSE OF THE "HIGH TUMOR STRAIN"

Twenty-five female mice of the dilute brown strain varying in age from 3 to nearly 17 months were studied (table 4). The structure of the mammary glands of these animals was strikingly different from that of the other strain and seemed to afford a possible basis for the special tendency to development of carcinoma in this race of animals.

The difference between the strains was already apparent at the age of 3 months. At this age the main ducts were similar to those in the C57 strain, although possibly more slender. The terminal branches, however, occurring both at the ends and at the sides of the ducts, were definitely more numerous (fig. 14).

By the age of 6 months the difference between the strains was completely established. The ducts themselves were still slender and showed no evidence of further extension, and microscopic examination confirmed the absence of any proliferation of the epithelial lining cells. The periductal connective tissue showed neither fibrosis nor lymphocytic infiltration.

The great change was in the development of innumerable new alveoli. They were found most characteristically in small groups along the sides and ends of the ducts. The degree of proliferation was, however, by no means uniform, and focal areas of large clusters occurred. The acini were now definitely club shaped, even globular, although in places the lack of a definite basement membrane gave in the gross preparation (fig. 15) a feathery outline to the duct with its covering of acini.

On microscopic examination of the mice at the age of 6 months acini were observed in clusters of three to four or more, often surrounding a dilated duct. These acini were small and distinct, often with a little pink-staining material in their lumens. The epithelium was still unexpectedly slight in amount considering what had been expected after examination of the gross preparations.

After the age of 12 months the ducts became almost unrecognizable in the gross mounts, being concealed by masses of new acini. In some animals the ducts were uniformly involved, the edges having a shaggy appearance (fig. 16). In a few the proliferation was still somewhat focal (fig. 17) and relatively normal segments of ducts remained with elsewhere solid clusters of alveoli producing opaque specks in the gross preparations—evidence that the gland tissue was no longer restricted to a single plane.

Microscopically examined, the ducts of the older mice were often slightly dilated and contained secretion. The acini were scattered in groups of five or ten or in aggregations of fifty or more. These clusters consisted of many well formed acini. Both the lumens and the cells themselves contained a little secretion (fig. 18). Between these glands there were sometimes masses of epithelial cells (fig. 19). Some new



Fig 14—Multiplication of acini in the mammary gland of a mouse of the "mammary tumor strain" at 95 days of age. Gross preparation



Fig 15—Indefinite margin of proliferating acinar masses in a mouse of the "high tumor strain" aged 210 days. Gross preparation, higher power.

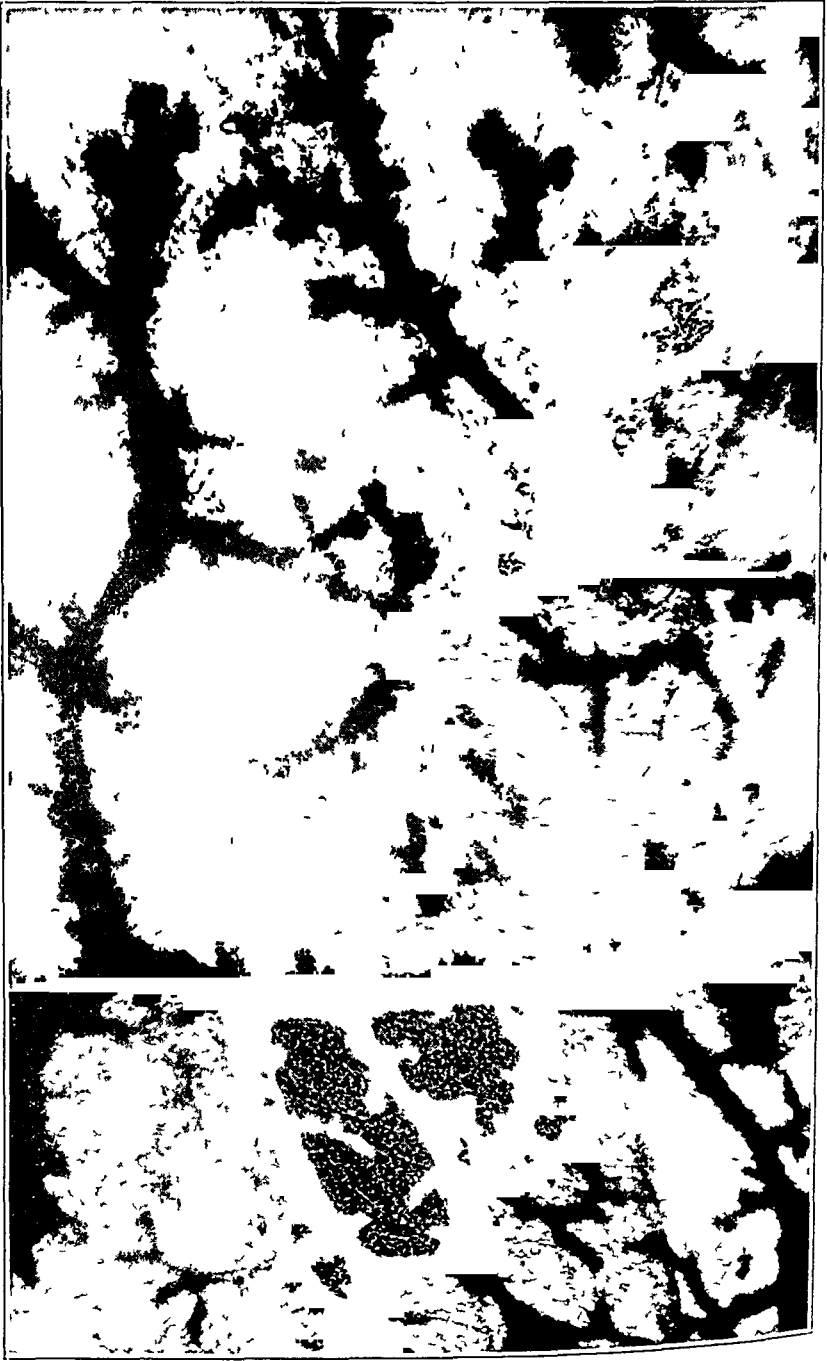


Fig 16—Uniform proliferation of the acini along the ducts in the mammary gland of a mouse of the "high tumor strain" aged 366 days Gross preparation



Fig 17—Focal proliferation of acini in the mammary gland of a mouse of the 'high tumor strain' aged 366 days. Gross preparation

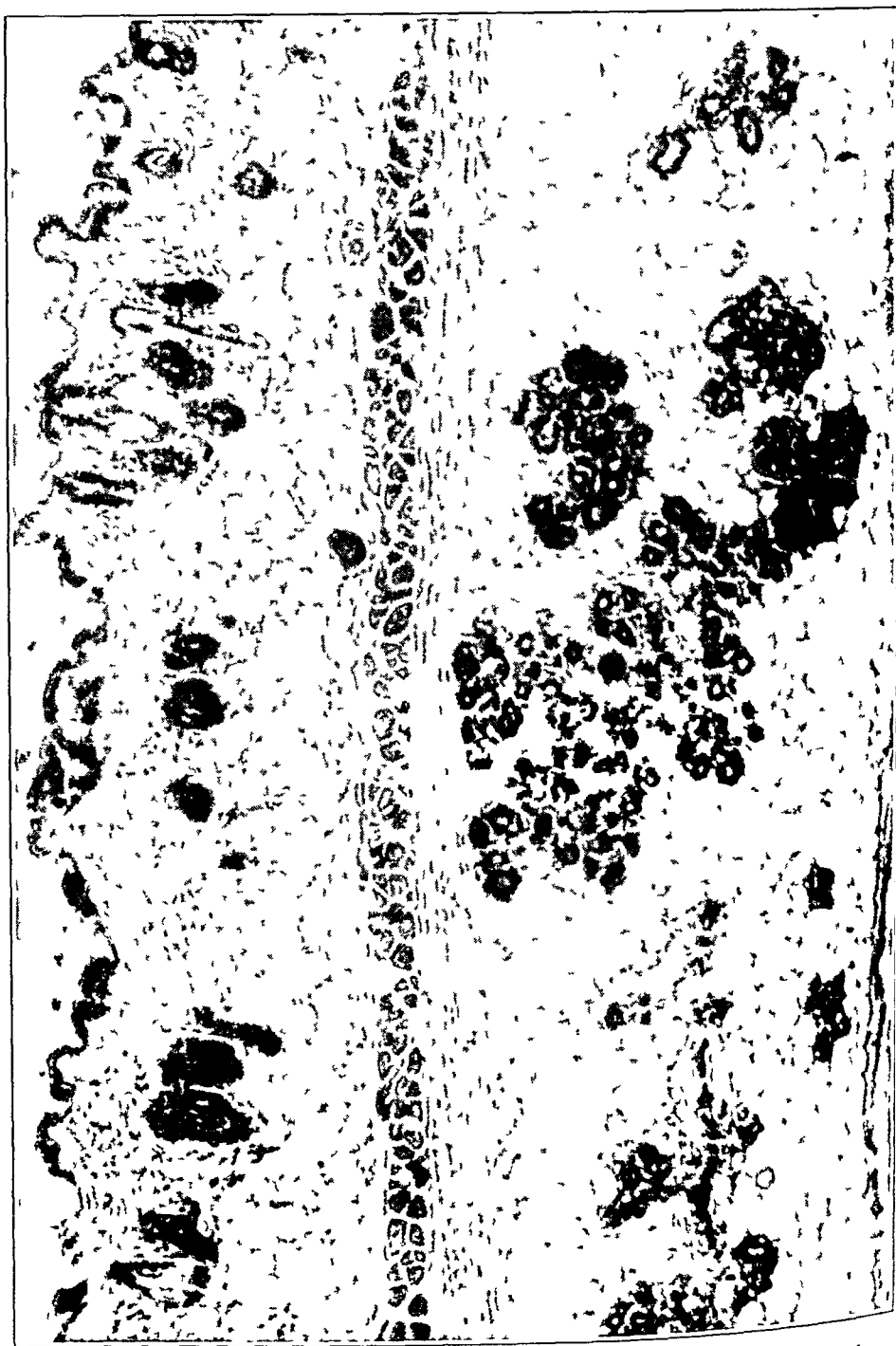


Fig 18—Cluster of well formed acini in the mammary gland of a mouse of the "high tumor strain" aged 414 days Microscopic preparation



Fig 19—Diffuse acinar proliferation in the mammary gland of a mouse of the 'high tumor strain' at the age of 428 days. Microscopic preparation.

connective tissue was doubtless formed to support the new acini, but there was nothing suggestive of pathologic fibrosis

This process of acinar proliferation was by no means consistent throughout the strain. A few animals at the age of 6 months showed more acinar development than did others twice as old. Such a difference may explain why certain animals of this strain have carcinoma and others do not. The cause of the difference in rate of development is perhaps to be found in the activity of the ovaries, which, as will be shown in a later section, varied in the different animals of the strain as regards both weight and number of corpora lutea. A correlation between marked epithelial growth in the mammary glands with heavy ovaries and many corpora lutea was suggested, but this was not proved by this series.

Carcinoma developed in 1 mouse of the 23 of this group, only 6 of which lived over twelve months. This tumor had a glandular arrangement and apparently developed on the basis of the abnormal acinar proliferation.

COMMENT

The difference in the mammary structure of these two strains of mice as early as the end of the third month of life is too striking to leave any doubt as to the accuracy of the observation. The facts noted apply, of course, only to the two strains studied, and it is by no means certain that a similar contrast exists between all strains with high and all with low incidence of tumor.

Gardner and Strong²⁸ studied the development of the mammary glands of ten strains of varying susceptibility and noted little or no difference. They concluded that no structural factor is associated with the intrinsic hereditary predisposition to mammary carcinoma in mice. They terminated their studies at about the one hundredth day, which was approximately the time at which our studies were begun. Fekete,²⁹ however, using the same strains as those employed in the present work, noted that during pregnancy certain glands of the "high tumor strain" persisted in proliferation at a time when all of the glands of the C57 strain had changed to functional activity and that after pregnancy regression in the dba strain was incomplete.

It appears, then, that the mammary glands in the female mice of these strains are similar at birth but that differences become apparent by the end of the third month. The hereditary factor to be sought is probably, therefore, not in the gland itself but in stimuli which make themselves evident in morphologic change in the mammary gland early in the life of the animal.

28 Gardner, W. U., and Strong, L. C. The Normal Development of the Mammary Glands of Virgin Female Mice of Ten Strains Varying in Susceptibility to Spontaneous Neoplasms, *Am J Cancer* **25** 282-290, 1935.

29 Fekete, E. A Comparative Morphological Study of the Mammary Glands in a High and Low Tumor Strain of Mice, *Am J Path* **14** 557-578, 1938.

It should be emphasized also that the early changes which lead eventually to the development of spontaneous carcinoma in mice affect essentially the peripheral portions of the mammary gland. There are practically no changes in the larger ducts, no papillomas, no stasis of secretions and no signs of inflammation, no cyst formation and no fibrosis. The pathologic lesions of the human breast which the picture most closely resembles are the rare isolated areas of acinar proliferation or adenosis.

CONCLUSIONS

1 Striking differences are noted as early as the third month of life between the structure of the mammary glands of two strains of mice differing as regards their susceptibility to mammary carcinoma.

2 The essential difference is a vast increase in the number of acini in the cancer-susceptible strain.

3 The human pathologic lesion which this picture resembles most closely is the rather infrequently encountered acinar proliferation, occurring in small foci and sometimes termed adenosis.

4 The more commonly described characteristics of so-called chronic cystic mastitis, the development of new fibrous tissue, the periductal inflammation and the intraductal epithelial proliferation, are not observed to occur spontaneously in mice.

5 The use of gross mounts of the mammary glands of mice of strains with a variable susceptibility to mammary carcinoma promises to be a valuable method for studying the possible stimulating or inhibiting effect of various chemical and biologic substances on the development of cancer.

IV ENDOCRINE CONSTITUTION OF TWO STRAINS OF MICE WITH TENDENCY TO SPON- TANEOUS MAMMARY CARCINOMA

In the previous section it was pointed out that although the mammary structure of a cancer-resistant and a cancer-susceptible strain of mice is probably identical in the young females, a greater complexity of acinar structure appears in the susceptible strain as early as the third month. This leads at once to the hypothesis that the ovary of the susceptible strain produces more estrogenic hormone and that this is the specific factor in the production of the tumor. Such a view is untenable, however, when it is remembered that when the same quantity of estrogen is administered from external sources to male mice, cancer will appear in the mammary glands of certain strains and not in those of others (Lacassagne³⁰). It appears probable, then, that the specific hereditary factor

³⁰ Lacassagne, A. Influence d'un facteur familial dans la production, par la folliculine, de cancers mammaires chez la souris male, *Compt rend Soc. de biol* 114 427-429, 1933.

resides neither in a primary anatomic peculiarity of the mammary gland nor in simple hyperfunction of the ovary

Considerable speculation has been devoted to the nature of this transmissible hereditary factor. Lacassagne³⁰ has suggested a difference in sensitivity of the mammary glands to identical quantities of estrogen. Cramer³¹ discussed the possibility of a greater susceptibility of the whole endocrine system, possibly due to a breakdown of some protective mechanism, and cited as evidence the "brown degeneration of the adrenals" observed by himself and Horning³²

To afford a general parallel with the endocrine studies reported on the cases of chronic cystic mastitis, certain material was collected on the endocrine status of the two strains of mice being studied. Some of the results give merely a basis for comment on previously reported work of others. Certain observations, notably those on the ovaries themselves, are essentially new.

ESTRUS CYCLES

It was natural to hope that some disturbance in the estrus cycles might be found as an indication of a disturbed ovarian function in the strain of mice which had spontaneous mammary carcinoma. Peculiarities of the estrus cycle in strains susceptible to cancer were reported in 1934 by Lacassagne³³. Subsequent investigations have, however, failed to corroborate his observations (Bonser,³⁴ Moskop, Burns, Suntzeff and Loeb,³⁵ Harde³⁶). In older animals at the time of onset of tumor the cycles are said to become infrequent, with long periods of diestrus (Allen, Diddle, Strong, Burford and Gardner³⁷).

31 Cramer, W. On Aetiology of Cancer of Mamma in Mouse and in Man. *Am J Cancer* **30** 318-331, 1937

32 Cramer, W., and Horning, E. S. Adrenal Changes Associated with Oestrin Administration and Mammary Cancer, *J Path & Bact* **44** 633-642, 1937

33 Lacassagne, A. Sur la pathogenie de l'adeno-carcinome mammaire de la souris, *Compt rend Soc de biol* **115** 937-939, 1934

34 Bonser, G. Comparison of Normal Oestrous Cycle and of Response to Administration of Oestrin in Two Strains of Mice Differing Greatly in Incidence of Spontaneous Mammary Cancer, *J Path & Bact* **41** 33-42, 1935

35 Moskop, M., Burns, E. L., Suntzeff, V., and Loeb, L. Incidence of Mammary Cancer and Nature of Sexual Cycle in Various Strains of Mice, *Proc Soc Exper Biol & Med* **33** 197-199, 1935. Burns, E. L., Moskop, M., Suntzeff, V., and Loeb, L. On the Relation Between Incidence of Mammary Cancer and Nature of Sexual Cycle in Various Strains of Mice, *Am J Cancer* **26** 56-68, 1936

36 Harde, E. Influence des hormones et des vitamines dans la production des adeno-carcinomes chez la souris, *Compt rend Soc de biol* **116** 999-1001, 1934

37 Allen, E., Diddle, A. W., Strong, L. C., Burford, T. H., and Gardner, W. U. Estrous Cycle of Mice During Growth of Spontaneous Mammary Tumor and Effects of Ovarian Follicular and Anterior Pituitary Hormones, *Am J Cancer* **25** 291-300, 1935

In the present investigation two characteristics of the cycle were considered first, the length of the cycle, and second, the part of the cycle occupied by estrus itself. The latter figure was obtained by cal-

TABLE 5—*Estrus Cycles in Two Strains of Mice of Variable Susceptibility to Mammary Carcinoma*

Age, Months	Number of Animals in Series		Average Length of Cycle in Days		Percentage of Estrus and Post estrus Spreads		Total Readings	
	C57	dba	C57	dba	C57	dba	C57	dba
3	6	15	6.1	7.1	40.3	30.6	144	373
4, 5, 6	4	13	8.6	7.0	26.8	26.4	205	808
7, 8, 9	7	19	8.1	7.2	36.4	32.1	253	1,018
10, 11, 12	3	16	5.7	7.8	42.6	26.7	204	986
13, 14, 15	3	10	5.2	9.0	46.0	18.5	87	546
Over 15	1	2	9.0	7.4	18.7	18.9	16	90

TABLE 6—*Comparison of Ovaries and Adrenals in Mice of Cancer-Susceptible and Cancer-Resistant Strains at Six Months*

C57 Strain						dba Strain					
Mouse No	Weight Gm	Weight of Adrenals Mg	Weight of Ovaries Mg	Number of Corpora Lutea per Largest Cross Section		Mouse No	Weight, Gm	Weight of Adrenals, Mg	Weight of Ovaries Mg	Number of Corpora Lutea per Largest Cross Section	
				A	B					A	B
06B	22.5	5.2	7.4	2	—	31	25.3	4.4	14.2	1	0
07B	22.2	4.6	8.0	3	2	36	24.1	5.4	19.8	3	3
09	22.1	10.2	15.6	3	2	46	28.2	3.2	22.6	5	4
10	21.7	9.2	6.8	5	3	47	30.0	4.6	18.2	12	11
13B	23.0	5.4	7.0	3	—	49	29.0	6.6	25.4	18	10
15B	23.5	5.0	9.4	5	1	50	25.6	6.6	15.0	1	1
18	21.6	4.0	6.0	—	—	56	27.5	5.4	22.8	6	6
21A	19.5	9.4	7.0	2	1	57	26.7	4.8	14.4	10	3
21B	22.5	4.2	6.8	2	1	58	28.5	4.8	23.0	12	10
22	24.5	10.0	13.6	3	0	59	26.9	5.0	13.6	3	2
23	25.1	5.6	8.8	3	3	60	29.1	6.2	23.4	4	3
27	24.0	4.6	8.4	0	0	78	24.1	8.0	25.2	3	2
30	22.0	3.8	6.4	0	0	79	26.5	10.6	28.2	7	4
31	22.4	5.0	6.2	2	2	86	25.5	10.8	24.8	4	2
33	23.7	5.6	8.8	2	1	87	28.5	6.8	32.2	15	7
36	23.0	14.4	11.8	2	1	88	23.1	9.2	21.4	11	4
37	24.5	4.6	10.8	—	—	89	25.1	15.2	24.2	2	2
38	22.2	4.6	6.2	1	0	91	25.5	4.6	31.8	8	7
43	21.2	6.8	6.2	0	0	93	20.2	8.2	13.8	12	8
48	23.0	10.2	11.2	3	2	94	27.3	15.2	33.8	22	19
75	21.1	6.6	10.4	3	2	99	21.2	8.6	16.2	—	—
76	26.1	4.4	13.6	3	3	130	22.0	8.2	27.2	13	8
95	23.8	8.8	11.8	3	2	140	20.8	13.2	24.2	13	5
96	22.5	8.8	6.8	1	—	143	18.5	4.0	30.0	11	4
105	22.1	13.6	7.8	1	0	150	22.9	7.4	23.2	6	2
112	22.5	10.6	—	4	2						
113	19.8	7.4	10.2	4	1						
Averages	22.8	6.9	9.0	2.4	1.3		25.3	7.5	23.1	8.5	5.4

culating the percentage of the daily vaginal spreads that showed only cornified cells or cornified cells with a few leukocytes. Table 5 shows that during the earlier months the duration of the cycle was about the same for the two strains. Later the cycles of the dba strain became longer. The length of estrus itself as determined by the percentage of completely cornified smears was somewhat greater for the C57 strain, indicating that the longer cycles of the dilute brown strain were due to

more days of diestrus. It is uncertain what significance can be placed on these observations, but the differences noted are perhaps to be correlated with the greater development of corpora lutea seen in the dba strain.

OVARIES

Early in the investigation we were impressed with the obviously greater size of the ovaries and the increased number of corpora lutea in

TABLE 7—Comparison of Ovaries of Mice of Cancer-Susceptible and Cancer-Resistant Strains at Various Ages

Age	C57 Strain				dba Strain			
	Mouse No	Weight of Ovaries, Mg	Corpora Lutea A	Corpora Lutea B	Mouse No	Weight of Ovaries, Mg	Corpora Lutea A	Corpora Lutea B
6 months	6A	7.4	0	0	12	12.0	6	4
	7A	7.6	2	2	13	20.0	9	8
	5	6.8	—	—	42	—	2	1
	11	18.8	2	—	62	14.8	12	9
	12	8.2	4	1	63A	—	2	1
	13A	9.8	3	2	63C	13.6	—	—
	14	12.0	4	2	64B	16.8	1	1
	15B	10.6	3	1	65	7.3	11	4
	52	8.6	2	1	66	12.8	8	7
	53	7.4	3	—	67	13.4	8	5
	54	9.4	5	1	71B	13.6	12	11
	55	8.8	4	2				
	56	7.4	—	—				
	51	—	0	0				
	73	—	3	2				
	Averages	9.4	2.7	1.3		13.8	7.1	5.1
7 12 months	23	—	0	0	01	—	3	3
	29	6.2	0	0	03	—	15	14
	50A	—	3	3	04	—	16	14
	50B	4.0	0	0	43	19.2	10	8
					53	15.9	12	9
					54	13.6	0	0
Averages		5.1	0.75	0.75	71A	34.6	5	4
						20.8	8.7	7.4
Over 12 months	19	4.6	1	0	33	23.3	14	11
	46	5.5	2	1	35	22.2	15	15
	74	6.7	5	1	46	17.7	11	10
					49	18.8	12	8
					60	25.4	7	4
					63B	26.0	18	17
					69	22.8	15	12
					70	29.0	8	6
Averages		5.6	2.7	0.67		23.2	12.5	10.4

the dilute brown strain. For that reason a number of additional animals were killed at the ages of 3 and 6 months to bring the number of pairs of ovaries examined to 44 for the C57 strain and to 54 for the dilute brown.

The average weight of a pair of ovaries from the dilute brown strain at 6 months of age was 23.1 mg., and from the C57 strain, 9 mg. (table 6). Only two pairs of ovaries of the cancer-susceptible strain weighed less than the heaviest ovaries of the cancer-resistant strain. The weight of ovaries obtained from smaller groups of animals at other ages indicated that the difference was constant (table 7).

Although serial sectioning was not resorted to, ten to twenty sections of each ovary were available. The number of corpora lutea in the largest available section of each ovary was tabulated. It must be remembered that the corpora lutea observable in the mouse ovary at one time represent not a single cycle but at least four, since it requires the duration of several cycles for those formed at one ovulation to disappear (Allen³⁸). Differentiation on histologic grounds between a regressing corpus luteum and a corpus albicans may be somewhat arbitrary. Nevertheless, the difference in the average number of corpora lutea in the two strains was too striking to admit the possibility of error.

At the age of 6 months (table 6) the average number of corpora lutea observable in the largest cross section of the larger ovary of the dba strain was 8.5, for the smaller ovary in that strain, 5.4. The comparable figures for the C57 strain were 2.4 and 1.3 respectively. The ovaries obtained from the two strains at other ages continued to show this difference (table 7).

Casual examination of the microscopic sections also indicated a remarkable dissimilarity. The ovaries of the dilute brown strain were often so filled with coalescing corpora lutea as almost completely to obscure the stroma (fig. 20). The ovaries of the C57 animals were usually obviously smaller and contained only one to four fairly large, discrete corpora lutea lying between large areas of stroma (fig. 21). Other characteristics, such as the number of follicles of various size and the amount of follicular atresia, offered no immediate points of contrast.

The increased number of corpora lutea in the cancer-susceptible strain may, of course, be interpreted as indicating greater stimulation of the mammary gland either by progesterin or by estrogen. If this difference were found consistently between all or most of the "high tumor incidence" strains on the one hand and of the "low tumor incidence" strains on the other, it would be a step toward explaining the greater epithelial activity in the mammary glands of the mice in which the incidence of tumor is high.

UTERUS

Microscopic sections made of the uteri showed little structural difference between the two strains. Weights were not determined, but those of the dilute brown strain appeared at autopsy to be, as a rule, the larger.

ADRENALS

Changes in the adrenal glands associated with the reproductive cycle are to be sought in a zone lying at the inner margin of the cortex and immediately about the medulla. This region, made up of small, dark

³⁸ Allen, E. The Oestrous Cycle in the Mouse, *Am J Anat* 30: 297-371, 1922.



Fig 20—Typical ovary of the cancer-susceptible strain at the age of 6 months

basophilic cells, is prominent in the young mouse and has been termed the x-zone. According to Howard-Miller's³⁹ studies, it appears in both sexes about the tenth day after birth. In the male the x-zone tends to disappear after the fourth week, in the female it persists somewhat longer. Progressive degeneration, however, gradually develops, so that at the age of 201 days there is absence of the x-zone in 60 per cent of unmated female mice and partial degeneration in the remainder. Castration in the male delays degeneration, pregnancy in the female precipitates it. Degeneration begins with vacuolization of the cells and



Fig 21—Typical ovary of the cancer-resistant strain at the age of 6 months

progresses to their complete disappearance, so that only a thin rim of connective tissue separates the cortex from the medulla. Deanesly⁴⁰ made somewhat similar observations. She found the x-zone at times intact in the unmated female at the age of 12 weeks and reported in a few cases the later development of a new cortical zone at the site of the x-zone, which she felt might be the homologue of the zona reticularis of

³⁹ Howard-Miller, E. Transitory Zone in Adrenal Cortex Which Shows Age and Sex Relationships, *Am J Anat* **40** 251-293, 1927

⁴⁰ Deanesly, R. Study of Adrenal Cortex in Mouse and Its Relation to Gonads, *Proc Roy Soc, London, s B* **103** 523-546, 1928

other adult animals Degeneration of the x-zone, according to her observations, occurs either by vacuolization or by an inconspicuous process of cellular degeneration

A possible significance of the x-zone in the etiology of mammary carcinoma in mice has been pointed out by Cramer and Horning²⁰ These workers observed that when an estrogenic substance was administered to normal mice of mixed strains there occurred in the peripheral part of the medulla and to a less extent in the cortex a necrosis and impregnation of masses of cells with lipoid material which on account of its appearance in unstained preparations they termed "brown degeneration" Occurring much later and having decidedly different morphologic characteristics, it is not to be regarded, however, as the same process as the apparently physiologic disappearance of the x-zone The process of "brown degeneration" observed by Cramer and Horning²⁰ occurred spontaneously only in a strain of mice (DZ) with a high

TABLE 8—Comparison of X-Zones of Adrenals of Cancer-Resistant and Cancer Susceptible Strains

Age, Months	Cancer Resistant				Cancer Susceptible			
	Normal X Zone	Beginning Degenera- tion	Advanced Degenera- tion	Complete Degenera- tion	Normal X Zone	Beginning Degenera- tion	Advanced Degenera- tion	Complete Degenera- tion
1	8	0	0	0	5	0	0	0
2	0	4	0	0	2	0	0	0
3	0	0	1	5	6	2	1	0
6	0	1	17	12	0	24	2	0
7 12	0	0	0	2	0	0	7	0
13 16	0	0	0	1	0	0	3	6

incidence of spontaneous mammary carcinoma The authors emphasized the importance of this lesion as perhaps one of the specific factors characterizing the exceptional susceptibility of the strain to mammary cancer

From animals to which no injections were given we have examined 50 pairs of adrenals of the C57 strain and 52 pairs of the dilute brown strain The organs were weighed but sectioned with a paraffin technic, which allows only an imperfect study of lipoid-containing cells Also, the majority of the adrenals studied were from mice only 6 months of age, so that the question of the spontaneous development of brown degeneration could not be thoroughly investigated In the 19 animals of the "high cancer strain" which were killed after the age of 6 months, it was, however, not prominent

There was considerable evidence (table 8) that some delay occurred in the disappearance of the x-zone in the animals of the dilute brown strain as compared to those of the C57 At 2 months the x-zone was nearly intact in both strains At 3 months considerable degeneration

had occurred in the C57 animals, but degeneration was only beginning in the dilute brown strain (figs 22 and 23) At 6 months, of 30 animals of the C57 strain, 1 showed early degeneration, 17 advanced



Fig 22—Typical adrenal of the cancer-susceptible strain at the age of 3 months

degeneration and 12 complete degeneration At the same age, of 26 animals of the dilute brown strain, 24 showed early degeneration and 2 advanced degeneration

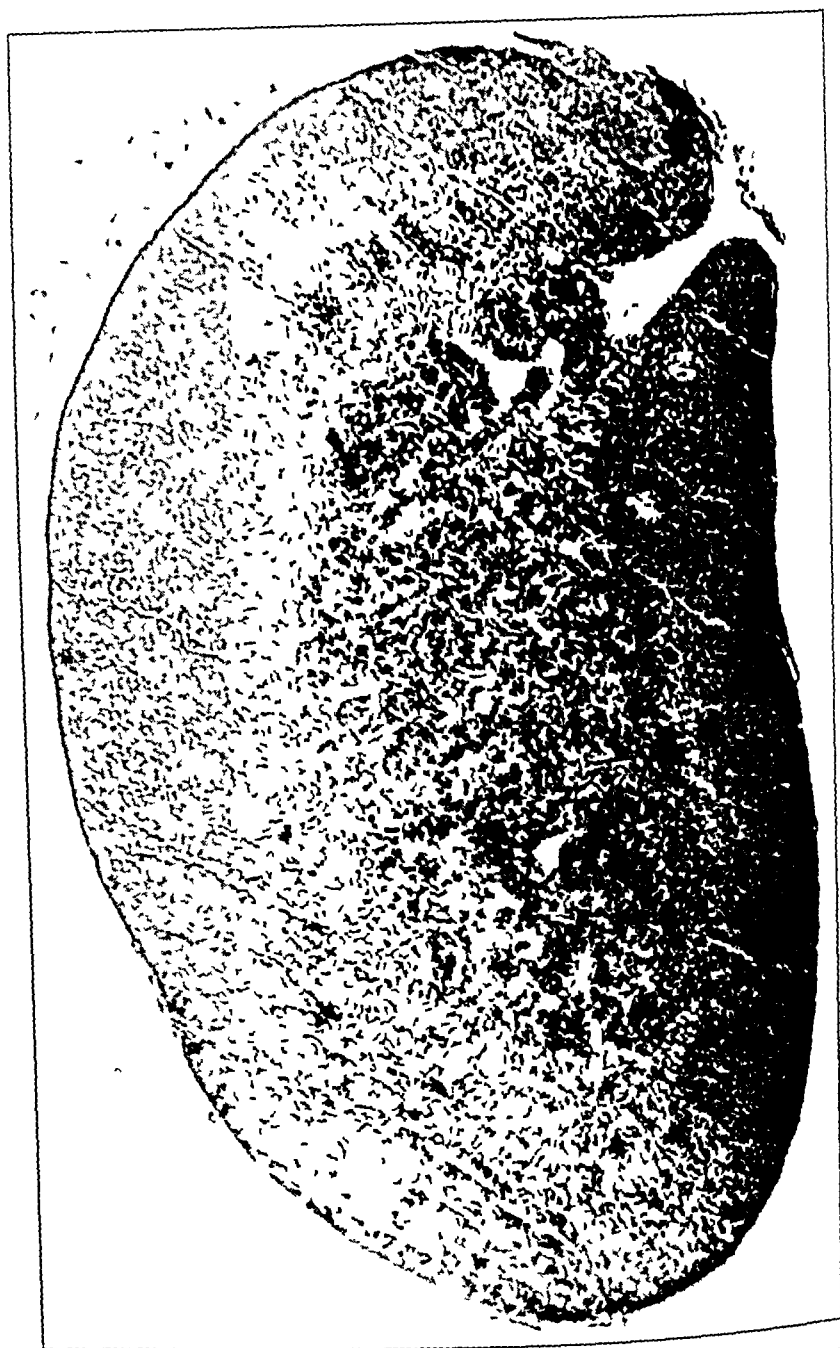


Fig. 23—Typical adrenal of the cancer-resistant strain at the age of 3 months

Vacuoles appeared during the course of degeneration, especially in the dilute brown strain. The difference in the manner of degeneration apparent in these two strains may explain why various observers in the past have disagreed as to the way in which the disappearance of the x-zone is brought about.

In a few instances in older animals, again especially in the dilute brown strain, clusters of dark cells were once more present in the region of the x-zone, often irregularly placed and sometimes connected by cords of similar cells to others immediately beneath the capsule. Some controversy has existed as to the possibility of a late regeneration of the x-zone, but the significance of these cells appearing in older animals just outside the medulla is made clear to us neither from study of our own material nor from a careful consideration of the literature.

The weight of the two adrenals at 6 months averaged 6.9 mg. for the C57 strain and 7.5 mg. for the dilute brown strain. It is doubtful whether this is a significant difference.

THYROID

Barry and Kennaway⁴¹ have recently reported a type of thyroid morphologic structure which they concluded is somewhat characteristic of mice with a high incidence of cancer. In examining the thyroid of several strains, they noted two types of gland. The thyroids of the CBA strain (of low cancer incidence) possessed a structure characterized by vesicles of relatively uniform size distended with eosinophilic colloid and lined by a uniform layer of low cuboidal or flattened cells with darkly staining nuclei. A second type was noted in Simpson's strain of albinos after treatment with estrone (theelin) and in untreated animals of Little's dilute brown strain. This type was characterized by great diminution and vacuolization of the colloid, expansion of the epithelial cells and loss of the uniform appearance of the gland, so that the peripheral vesicles often contained the most colloid, the central ones being small and collapsed.

In studying the thyroids in this series, both of the normal controls and of the experimental animals to be described in a later section, the entire gland was removed intact and sectioned histologically with the larynx in the center. A total of 35 glands from the C57 and 41 from the dilute brown strain were thus studied histologically for the normal morphologic thyroid structure of the animal to which no injections had been given.

⁴¹ Barry, G., and Kennaway, E. L. Structure of the Thyroid in Mice of Different Strains, *Am. J. Cancer* **29** 522-529, 1937.

The results showed that the glands of the two strains could not with any consistency be separated from each other when treated as "unknowns." All of the untreated animals of the C57 strain showed the first type of gland described by Barry and Kennaway,⁴¹ with moderately large vesicles of fairly uniform size (fig 24). The majority of the animals of the dilute brown strain also showed this type of gland, about 25 per cent exhibiting the small collapsed central vesicles of Barry and Kennaway's second type (fig 25).

PITUITARY

Changes in the anterior lobe of the pituitary gland after administration of an estrogen have been reported by many writers and will be discussed later. Differences in the morphologic appearance of the glands of the untreated animals of low and high susceptibility to cancer might be expected on account of the dissimilarity of the ovaries.

The pituitaries of all of the untreated animals of both strains were studied by serial section. With a simple hematoxylin-eosin staining technic no consistent differences between the strains could, however, be noted.

CONCLUSIONS

- 1 A difference in the endocrine glands of two strains of mice having such extremely divergent mammary structures as those described in the previous section is *a priori* probable.

- 2 The strain with excessive mammary proliferation (dba) has been shown by this study to have a much larger ovary and one containing many more corpora lutea than has the cancer-resistant strain (C57).

- 3 Less striking differences were probably present in the adrenal and perhaps in the thyroid.

- 4 Characteristic differences in the anterior lobe of the pituitary may exist but must be sought with a more intricate histologic technic than was employed in this work.

- 5 It must, of course, be remembered that neither of the strains studied is necessarily representative of all the cancer-susceptible or of all the cancer-resistant groups.

- 6 The differences in the ovaries of the two strains should, however, draw attention once more to morphologic examination of the ovaries of women with hyperplastic and neoplastic disease of the breast.



Fig 24—Thyroid of the cancer-resistant strain with distended peripheral alveoli at 6 months



Fig 25—Thyroid of the cancer-susceptible strain with small collapsed central alveoli at 6 months

V LESIONS RESEMBLING CHRONIC MASTITIS PRODUCED BY THE INJECTION OF ENDOCRINE SUBSTANCES INTO TWO STRAINS OF MICE DIFFERING IN THEIR SUSCEPTIBILITY TO MAMMARY CARCINOMA

In previous sections it has been established that of the two strains of mice used, the black (C57) goes through life, if unmated, with a relatively simple mammary structure consisting almost entirely of ducts, while the other, the dilute brown strain, becomes distinguishable as early as the third month by an enormous proliferation of new acini. In addition, it was noted that the ovaries of the dilute brown strain are consistently larger and contain more corpora lutea.

Theories as to the origin of human chronic mastitis assume, as a rule, the simple overproduction of one hormone producing a so-called imbalance. In the experiments to be reported, the effects of an excess of four different endocrine principles on two strains of mice with different inherent tendencies to mammary proliferation were investigated. These experiments were directed not toward the production of mammary carcinoma, which has been the object of study of many investigators, but toward the development of benign lesions and particularly toward a study of their morphologic similarity to one of the forms of human chronic mastitis.

Two principles were followed which distinguish these experiments from studies of normal physiology. No endocrine organs, such as the ovary or the hypophysis, were first removed, so that the endocrine substances injected represented clearly an excess and not a substitution. Secondly, the injections were not discontinued at the time when a physiologic effect might have been produced but were given for periods up to five hundred days, representing a considerable part of the animal's normal life span. Both of these conditions appear to parallel current hypotheses for the production of the human disease.

PREVIOUS WORK ON THE EXPERIMENTAL PRODUCTION OF CHRONIC MASTITIS

Investigations claiming the artificial production of chronic mastitis in animals fall into two classes: (a) those undertaken in a definite attempt to produce chronic cystic mastitis and (b) those carried out simply to study the effect of the injection of various estrogenic compounds.

a. The first investigation of the former group was that of Goormaghtigh and Amerlinck,⁴² who injected into 12 mice daily for from

⁴² Goormaghtigh, N., and Amerlinck, A. Production de formations adenomateuses mammaires par des injections prolongees de folliculine. *Compt rend Soc de biol* 103 527-529, 1930.

one to nine months 61 at units of an estrogenic substance, producing dilatation of the ducts, increased formation and retention of secretion and cystic and solid glandular hyperplasia in 75 per cent of their animals. These changes they concluded to be consistent with the lesions of Reclus' disease. Somewhat similar results were reported by Burrows,⁴³ who applied a solution of estrogen in benzene to the interscapular region of mice at biweekly intervals and noted proliferation of the mammary ducts, formation of small cysts and a stage of hyperplasia comparable in his opinion to chronic cystic hyperplasia of the human breast, for which he offered the suggestive name of "oestrogenic mastopathy."

The view of chronic mastitis as due simply to an increase in estrogen has been modified by experiments with other endocrine factors. Cramarossa⁴⁴ reported having produced mammary hyperplasia with corpus luteum, and Wieser⁴⁵ claimed to have produced it with corpus luteum in combination with other factors. The work of Herold and Effkemann⁴⁶ contradicts these results. They reported first the development of cysts following the injection into rats of 50 to 250 international units of estrogenic substance daily for short periods and the later appearance of epithelial proliferation, "pale epithelium" and fibrosis of the stroma. These changes, however, were prevented by administration of the corpus luteum hormone in sufficient quantities.

Workers with rabbits have been more cautious in their conclusions. Fifer⁴⁷ stated the opinion that it is the resting stage, that is, the male, virgin female and postlactatory mammary glands, which exhibits the pathologic picture known in the human breast as chronic cystic mastitis, with cysts lined by abnormal epithelium, areas of hyperplasia, cellular infiltration and proliferation of the stroma. According to Fifer, during periods of functional activity the gland assumes a more orderly appearance. He concluded that there is a tendency to growth on the part of the epithelial cells, which need a hormone to control their orderly development. MacDonald,⁴⁸ injecting estrogenic substances (theelin and

43 Burrows, H. Pathological Changes Induced in the Mamma by Oestrogenic Compounds, *Brit J Surg* **23** 191-213, 1935.

44 Cramarossa, V. Ormone corpo luteo e iperplasie sperimentali della mammella (in rapporto all'istogenesi della malattia cistica di Reclus), *Riv ital di ginec* **16** 93-112, 1934.

45 Wieser, C. Ueber die hormonale Beeinflussung der Mausebrustdrüse. Ein Beitrag zur Frage der Ätiologie der reclusischen Krankheit, *Arch f Gynäk* **154** 548-564, 1933.

46 Herold, L., and Effkemann, G. Beziehungen des Follikelhormons zu pathophysiologischen Wachstumsorganen der Brustdrüse, *Arch f Gynäk* **163** 85-93, 94-101, 309-315 and 673-679, 1936.

47 Fifer, C. L. The Breast Lesion in Rabbits Resembling Chronic Cystic Mastitis, *Arch Surg* **29** 555-559 (Oct) 1934.

48 MacDonald, I. G. The Response of the Mammary Gland to Prolonged Stimulation with Ovarian Hormones, *Surg, Gynec & Obst* **63** 138-144, 1935.

"progynon-B") in daily doses of 50 rat units, noted at first some pathologic changes in the lining of the ducts, which later, after six months of continuous injection, had largely disappeared. Estrone (theelin) in combination with corpus luteum extract produced both ductal and acinar growth with some secretion and distention of the ducts. He concluded, however, that on the basis of present evidence estrogen and progestin do not produce specific pathologic lesions, cystic disease or adenosis.

b During the course of the series of experiments to show the effect exerted by estrogen on the incidence of mammary carcinoma in male mice, some information has incidentally accumulated on the proliferative changes in the ducts and acini which precede the development of carcinoma. Observation indicates the variable response to be expected depends partly on the strain of animal and partly on the precise estrogenic substance used.

The importance of the strain has been considered by several investigators. Gardner and his co-workers⁴⁹ observed that estrone (theelin) would cause a gradual growth of the mammary rudiments of male mice for sixty to seventy-five days but that after the end of this period there was little change and that, furthermore, no differences were observed in the rate or extent of development induced in the mammary ducts of three strains differing in susceptibility to spontaneous development of tumor. Bonser,⁵⁰ using two strains of variable susceptibility to mammary cancer, administered ketohydroxyestrin benzoate (estrone benzoate) by injection of weekly doses of 300 to 500 international units and by painting with an 0.01 per cent solution in benzene. Unexpectedly, it was the cancer-resistant strain which showed the earlier and more widespread proliferation of acini and cystic distention of the ducts with secretion. In the cancer-susceptible strain there was some growth of the ducts but less distention and secretion and only localized proliferation of acini.

The variable effects of different estrogenic compounds have been reported by several workers. Burrows⁵¹ noted that with estrone (theelin), equilenin and the methyl ether of estrone there were proliferation of the mammary ducts and a moderate development of acini. Estra-

⁴⁹ Gardner, W. U., Diddle, A. W., Allen, E., and Strong, L. C. The Effect of Theelin on the Mammary Rudiments of Male Mice Differing in Susceptibility to Tumor Development, *Anat. Rec.* **60**: 457-475, 1934.

⁵⁰ Bonser, G. The Effect of Oestrone Administration on the Mammary Glands of Male Mice of Two Strains Differing Greatly in Their Susceptibility to Spontaneous Mammary Carcinoma, *J. Path. & Bact.* **42**: 169-181, 1936.

⁵¹ Burrows, H. A Comparison of the Changes Induced by Some Pure Oestrogenic Compounds in the Mammae and Testes of Mice, *J. Path. & Bact.* **42**: 161-168, 1936.

diol and equilin had little influence on development of the ducts, but a powerful one on the production of acini. Estriol (theelol), however, favored the development of both ducts and acini. Lacassagne,⁵² in comparing the action on the mammary glands of various substances, noted the greatest effect from estrone, less from equilin and the least from equilenin. What they regarded as a definitely abnormal type of proliferation was observed by Gardner and his co-workers⁵³ in the mammary glands of male mice treated with a benzoated estrogen. In contrast to simple growth of the mammary duct system, there occurred an extensive development of alveolar tissue, with some hyperplastic lobules resembling small adenomas, and areas of overgrowth of connective tissue.

The effect of prolonged stimulation by other than estrogenic substances on the development of abnormal types of proliferation has been less studied. Gardner and Hill⁵⁴ have recently noted proliferation of the ducts in male mice when the corpus luteum hormone was given alone or in combination with estrone (theelin). Howard,⁵⁵ injecting acid extracts of the anterior lobe of the pituitary gland of sheep into 6 rats for periods up to one hundred and seventy-nine days produced periductal fibrosis with fibroadenomatous areas but neither alveolar nor lobular development. The injection of gonadotropic substance from the blood of pregnant women produced a different reaction, hyperplasia of the gland with the appearance of secretion, but later regressive changes, small milk cysts and adenomatous areas. Since only a small number of animals were used, some of the supposed effects may have been accidental and spontaneous.

When one compares the list of lesions reported in these experiments with those noted in the first section as observable in a typical series of cases of chronic cystic mastitis, one is impressed with many discrepancies. Particularly are the fundamental processes of fibrosis and hyperplasia of the ductal epithelium largely lacking from the list of lesions artificially produced. It is particularly important, then, to reexamine the lesions produced in the mouse mammary glands by administration of various endocrine substances and to determine how far they are comparable with the lesions tabulated for the human disease and produced by some still unknown agent.

52 Lacassagne, A. A Comparative Study of the Carcinogenic Action of Certain Oestrogenic Hormones, *Am J Cancer* 28 735-740, 1936

53 Gardner, W. U., Smith, G. M., and Strong, L. C. Stimulation of Abnormal Mammary Growth by Large Amounts of Oestrogenic Hormone, *Proc Soc Exper Biol & Med* 33 148-150, 1935

54 Gardner, W. U., and Hill, R. T. Effect of Progesterin upon the Mammary Glands of the Mouse, *Proc Soc Exper Biol & Med* 34 718-720, 1936

55 Howard, N. J. Comparative Studies of Gonadotropic Hormones, *Proc Soc Exper Biol & Med* 34 732-734, 1936

METHODS

The treated animals, again of a cancer-susceptible (dba) and a cancer-resistant strain (C57), were cared for and the specimens prepared as has already been described for the normal animals. Vaginal smears were made and recorded daily. The mammary glands of the left side were sectioned histologically, while those of the right side were dissected out in their fascial layers stained and mounted. The ovary, uterus, adrenal, thyroid and pituitary were examined microscopically.

EFFECT OF INJECTIONS OF ESTRONE (AMNIOTIN) ⁵⁶

A total of 29 animals received one injection weekly of 800 international units of amniotin in oil injected beneath the skin of the back. Occasional injections were omitted when the animals became infected.

TABLE 9—Duration of Injections and Total Dose of Estrone (Amniotin)

Cancer Resistant Strain (C57)			Cancer Susceptible Strain (dba)		
Mouse Number	Injection Period in Days	Total Units Injected	Mouse Number	Injection Period in Days	Total Units Injected
68	33	3,080	76	39	3,840
15	74	5,640	77	39	3,840
92	90	8,230	71	105	12,000
03 A	119	9,480	01	151	17,600
42	119	9,480	03	151	17,600
03 B	112	12,500	36	158	18,400
71	123	14,400	05	233	26,400
73	130	15,200	10	233	26,400
02	138	16,000	41	292	33,600
76	142	16,800	39	292	34,400
24	179	21,600	60	311	34,400
05	229	26,400	68	354	38,400
04	241	28,000	15	372	43,200
28	247	28,000	74	388	44,800
78	323	37,600			

or some of the oil was unabsorbed. The time during which the injections were given and the total quantities injected are shown in table 9.

Cancer-Resistant Strain (C57)—In the cancer-resistant strain an early and persistent effect was dilatation of the main and sometimes of the second branches of the ducts. This was evident both in the gross and in the microscopic preparations but was not invariably present. No proliferation of the lining of the ducts occurred. The response of the acini of the C57 strain to amniotin was not striking, and in some animals it appeared to be absent (fig 26). In most animals, however, even those treated for a shorter period, a definite increase of the finer branches or acini at the ends of the ducts was evident. Microscopic examination of these acini showed only well formed units with possibly a little excessive secretion but no suggestion of atypical proliferation (fig 27).

⁵⁶ The amniotin, follutein and prolactin required for this study were supplied by Dr J A Morrell, of E R Squibb and Sons.

In some animals, especially in the gross preparations, there was evidence of an increase in cellularity of the tissues immediately beneath the basement membrane of the ducts (fig 28). This increased cellularity was due in part to connective tissue cells and in part to infiltration with lymphocytes. It is not, of course, clear whether this is a direct response to the injected substance or is a reaction to the inflammation from the secretion within the ducts. Conditions identical with human mammary disease were thus not produced in this strain by this substance, the only effect being slight acinar proliferation, a little dilatation of the ducts and rarely some periductal inflammation.

Cancer-Susceptible Strain (Dilute Brown)—The mammary glands of the dilute brown strain showed after the injection of estrone (theelin) simply an exaggeration of their inherent proliferative tendencies. The ducts became dilated, though possibly less so than in the C57 strain. There was no evidence of increase in their length, and even after over a year of injections and in the presence of carcinoma elsewhere in the gland, hyperplasia of the lining of the duct was as a rule absent (fig 29). In 2 animals, each 7 months and 11 days old, after injection of 17,600 international units some reduplication of the lining of several of the larger ducts was a possibility (fig 30).

Proliferation of the acini commenced at once, however, and after six weeks of injections (fig 31) was more or less universal. In the gross the acini were found to cover the ends and sides of the ducts, producing fanlike configurations, or appeared in concentrated clusters. Usually the acini in the gross had indefinite feathery edges, but occasionally dilated ones produced sharply circumscribed globular structures (fig 32). The latter form was apparently the result of distention with secretion.

Under the microscope the acini were seen to occur in clusters of increasing size as the duration of injection and the age of the animal advanced. They were sometimes dilated, with a little secretion in the cells and in the lumens of the ducts (fig 33). Often, however, they were collapsed, with sheets of cells lying between them in which tubular forms could barely be recognized (fig 34). Of the 6 animals allowed to live beyond the age of 12 months 3 had mammary carcinoma.

The chief difference between these treated animals of the dilute brown strain and the normal animals was, therefore, the earlier and more marked acinar development and perhaps a slight increase in dilatation of the ducts and secretion in the tubules. The continued freedom of the larger ducts from any striking proliferation was noteworthy. The inherent tendency of new acini to develop overshadowed any specific changes produced by the exogenous estrogen.



Fig 28—Connective tissue and lymphocytes beneath the ducts in a mouse of the "low tumor strain" at the age of 8 months after 21,600 units of estrone had been given Gross preparation



Fig. 29—Absence of hyperplasia of the ducts in a mouse of the 'high tumor strain' at the age of 15 months, after 43,200 units of estrone had been given. Microscopic preparation.

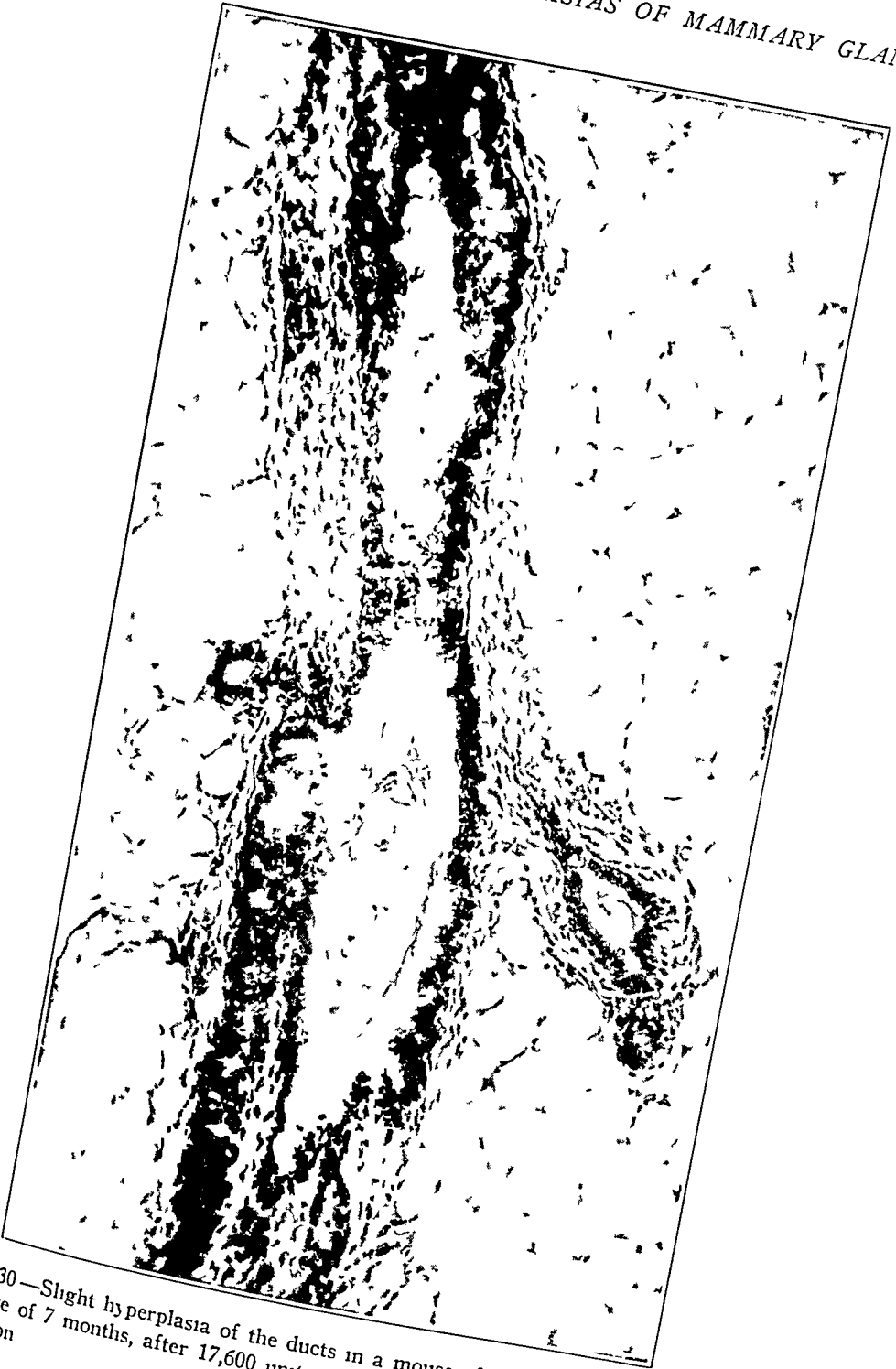


Fig 30—Slight hyperplasia of the ducts in a mouse of the 'high tumor strain' at the age of 7 months, after 17,600 units of estrone had been given Microscopic preparation



Fig 31—Early acinar proliferation in a mouse of the "high tumor strain" at the age of 3 months, after 3,840 units of estrone had been given. Gross preparation.



Fig. 10.—Sharp margins of dilated secretion-containing acini in a mouse of the "high tumor strain" at the age of 15 months after 44,800 units of estrone had been given. Gross overreaction.



FIG. 33.—Dilated and proliferated acini in a mouse of the "high tumor strain" at the age of 15 months after 44 800 units of estrone had been given. Microscopic preparation.



Fig 34—Multiplication of acini with solid areas of epithelial cells in a mouse of the "high tumor strain" at the age of 10 months, after 26 400 units of estrone had been given Microscopic preparation

EFFECT OF INJECTION OF ESTRADIOL BENZOATE
(OESTROFORM B)

The dose of estradiol benzoate was 1,000 international units weekly, given in a single injection to 11 mice of the C57 and 13 of the dba strain (table 10). Estradiol (dihydroxyestrin) is perhaps five to ten times as active biologically as ketohydroxyestrin, and the effectiveness of the preparation used was perhaps further increased by the delayed absorption of the benzoated form.

This increased potency was indicated by the rapid development of pyometra and the death of the first lot of animals treated with this substance. No such difficulty had been encountered with the animals given injections of amniotin. The animals of the second series (the series here reported) were all therefore subjected to hysterectomy before

TABLE 10—*Duration of Infections and Total Dose of Estradiol Benzoate*

Cancer Resistant Strain (C57)			Cancer Susceptible Strain (dba)		
Mouse Number	Injection Period in Days	Total Units Injected	Mouse Number	Injection Period in Days	Total Units Injected
04	42	6,000	65	52	7,000
01	49	7,000	64	54	7,000
09	119	17,000	67	99	15,000
03	119	17,000	98	164	27,000
70	124	18,000	02	189	27,000
83	124	18,000	71	190	28,000
84	269	32,000	88	217	31,000
80	279	33,000	07	217	31,000
81	279	33,000	69	277	40,000
02	304	35,000	76	277	40,000
08	304	43,000	89	293	43,000
			81	303	44,000
			79	304	44,000

the injections were begun. After this the treatment was comparatively well borne, although there were some premature deaths and one or two abscesses were encountered at autopsy near the ovary, possibly in remnants of the fallopian tubes.

Cancer-Resistant Strain—There was little to distinguish the effects of estradiol benzoate from that of estrone on the mammary glands of the C57 strain. The ducts were occasionally although not uniformly dilated (figure 35 representing an extreme example). The lumens of the ducts contained a little secretion, but there was usually no sign of hyperplasia of the lining of the ducts even after long periods of injections. Periductal fibrosis was slight.

The acini were moderately increased in number over the normal but this appeared to be no more marked than in the animals treated with amniotin. There was almost as much acinar development at 4 months after 7,000 units had been given, as at 13 months, after 43,000 units. It was especially interesting to note that the degree of acinar prolifer-



Fig 35—Dilatation of duct in a mouse of the "low tumor strain" at the age of 6 months, after 18,000 units of estradiol benzoate had been given. Gross preparation

ation in this cancer-resistant strain after injections of estradiol was much less than that accompanying the normal acinar development of the untreated mice of the cancer-susceptible type

In only 1 case was there a local area in which clusters of acini occurred somewhat suggestive of the dba type (fig 36). Microscopic sections from the glands of this mouse showed also dilated ducts, an increase in the number of acini and possibly slight hyperplasia of the epithelium of the ducts. The somewhat unequal response of different members of these strains is not surprising, for it should be remembered that even in a supposedly "cancer-free" line an occasional mammary carcinoma develops.

Cancer-Susceptible Strain—The ducts of the dilute brown strain treated by estradiol benzoate showed certain pathologic changes. Nearly all were dilated, and in 5 there was some hyperplasia of the lining (fig 37). Also there occurred in 1 mouse clusters of small dilated tubules, perhaps to be interpreted as newly formed ducts (fig 38).

The most striking changes in the ducts of the animals which received estradiol benzoate for long periods were the signs of a chronic state of retained secretion. The cells of many of the acini were swollen. Pink amorphous material was present in many of the ducts, and occasionally cells with a yellowish cytoplasm lay free in the lumen (fig 39), resembling in many respects the fat-containing cells observed at times in the human disease.

Signs of a reaction to this secretion within the ducts was evident in the surrounding tissues. Increase in fibrous tissue was present in several animals and was marked in 1 case (fig 37). Moderate lymphocytic infiltration was not uncommon. Finally, about the ducts of 1 animal were masses of pale hexagonal cells with large distinct nuclei, apparently endothelial leukocytes (fig 40).

The acini had proliferated greatly in all of these animals, possibly more so than in those treated with estrone. Grossly these multiplying acini sometimes took the form of great feathery masses covering the entire stem of the duct (fig 41), while at other times the development was more focal. Careful examination of the margins of the acinar masses under the low power microscope showed that sometimes there was a relatively sharp basement membrane, whereas in other places the edge was quite diffuse (fig 42).

Some variation in the degree of response was evident both between different animals and in different parts of the same gland. In some mice treated for nearly a year, considerable segments of duct were nearly free of acini, in contrast to the almost uniform proliferation sometimes present after only a few weeks of treatment. It was gen-



Fig 36—Localized intense acinar proliferation (rarely seen) in a mouse of the "low tumor strain" at the age of 11 months, after 33,000 units of estradiol benzoate had been given Gross preparation



Fig 37—Periductal fibrosis and slight hyperplasia of the ducts in a mouse of the "high tumor strain" at the age of 8 months, after 28,000 units of estradiol benzoate had been given. Microscopic preparation.

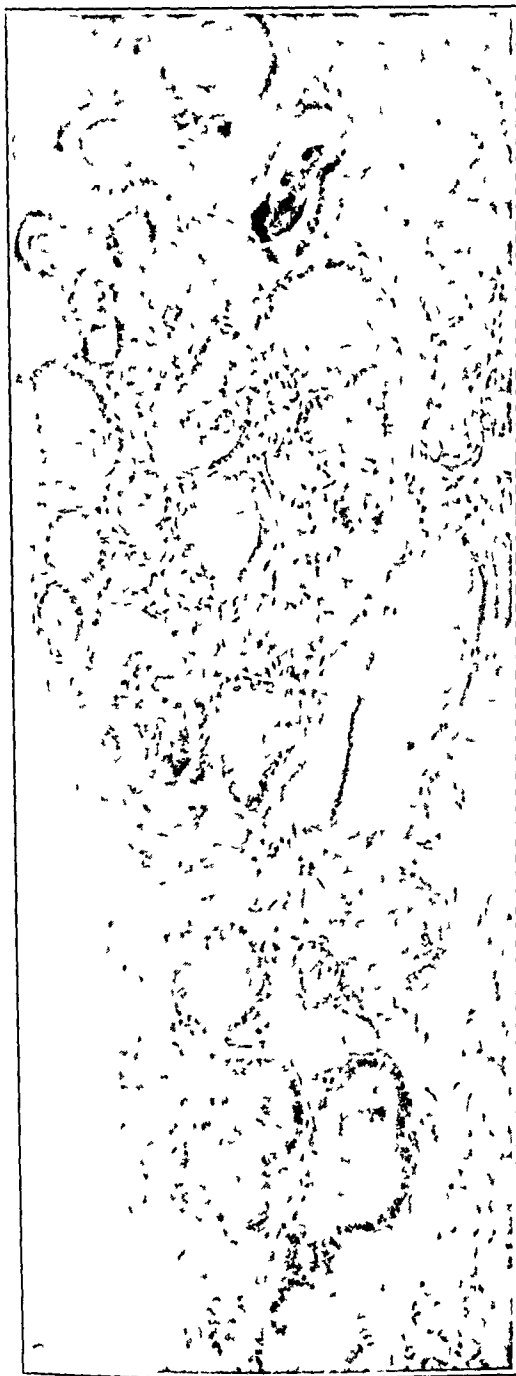


Fig 38—Proliferated clusters of tubules, possibly ducts, in a mouse of the 'high tumor strain' at the age of 9 months, after 28,000 units of estradiol benzoate had been given. Microscopic preparation.



Fig 41—Generalized acinar proliferation in the mammary glands of a mouse of the 'high tumor strain' at the age of 12 months, after 43,000 units of estradiol benzoate had been given. Gross preparation.



Fig 42—Diffuse margin of acinar clusters suggesting infiltration in a mouse of the "high tumor strain," aged 9 months, after 31,000 units of estradiol benzoate had been given Gross preparation

cially true, however, that the larger masses of acini occurred in the older animals, whereas in the younger, although proliferation was universal, no large clumps had yet been formed.

Under the microscope the acini were found in large groups. Particularly in the younger animals the tubules were of medium size, dilated with an acidophilic secretion and composed of a regular ring of cuboidal cells. This type predominated in animals 6 months of age. Later, smaller alveoli, collapsed and lumenless, with small cells composed mostly of nuclei, were commoner. Between these acini, sheets of diffusely growing epithelial cells, some showing mitosis, were present. One type of proliferation with several acini growing together in a small cluster, their lumens partly filled with cells, closely resembled certain forms of abnormal acinar proliferation in women (fig 43).

Palpable cancer developed in 2 of the 3 animals which lived to be over 1 year old and in 2 of the 4 animals which lived nine to ten months. In the mounted specimens from the other animals of these ages opaque islands of multiplying acini probably indicated the beginning of multiple small malignant areas.

In summarizing the effects of estradiol benzoate on the cancer-susceptible strain, it appears that the principal effect is still simply acceleration of the normal acinar proliferation and the eventual development of carcinoma on this basis. There is in addition, moderate hyperplasia of the duct epithelium, but the chief changes in this region are periductal, apparently the result of stasis of secretion in the lumens. In this respect the mammary tissue from the animals treated with estradiol resembles somewhat the type of mammary disease seen in women in which the chief features are retained secretion, periductal inflammation and moderate proliferation of the cells lining the ducts. Neoplasms of the ducts, in the sense of papillomas, were certainly not produced.

EFFECT OF INJECTION OF GONADOTROPIC SUBSTANCE FROM URINE OF PREGNANT WOMEN (FOLLUTEIN, SQUIBB)

The dose of gonadotropic substance was 30 rat units given twice weekly to a series of 11 animals of the resistant and 17 of the susceptible strain (table 11). No difficulties were encountered with the giving of this material for as long as thirty-four weeks.

Cancer-Resistant Strain—No proliferation of ducts or acini resulted from the injection of this gonadotropic substance. The character of the gross and microscopic sections as a rule fell within the limits of what had been observed for the untreated animals. In 2 animals of the cancer-resistant strain exceptions to these findings were noted. In each the larger ducts were greatly dilated and contained secretion,



Fig 43—Coalescing acinar clusters in a mouse of the 'high tumor strain' at the age of 12 months, after 40,000 international units of estradiol benzoate had been given Microscopic preparation

while numerous small acini, sometimes in tiny clusters, were also present. Since this was noted in only 2 animals, these changes may represent individual peculiarities rather than the specific effect of the substance injected.

Cancer-Susceptible Strain—This substance had also no effect on the evolution of the excessive mammary epithelial development normal to the cancer-susceptible strain. All of the formations described for the control animals of this group were here repeated (fig 44). Carcinoma developed as a palpable growth in the only animal surviving twelve months and in a second, which survived eleven months.

TABLE 11—*Duration of Injections and Total Dose of Gonadotrophic Substance from Urine of Pregnant Women (Follutem)*

Cancer Resistant Strain (C57)			Cancer Susceptible Strain (dba)		
Mouse Number	Duration of Injection Period in Days	Total Injections in Rat Units	Mouse Number	Duration of Injection Period in Days	Total Injections in Rat Units
33	40	700	92	36	270
23 A	78	1,340	71	29	500
12	235	2,040	66	35	600
29	235	2,040	02	124	1,020
28	274	2,370	22	124	1,020
25	288	2,490	20	71	1,220
15	316	2,730	04	71	1,220
23 B	316	2,730	09	148	1,280
85	379	3,270	08	164	1,350
01	397	3,420	79	169	1,410
19	397	3,420	19	261	2,100
			57	232	2,370
			28	259	2,400
			24	270	2,520
			03	327	2,850
			33	330	2,850
			29	375	2,850

In 1 or 2 of the younger animals it appeared possible that the acinar proliferation was a little less than normal. In 1 case particularly the ducts showed almost no acinar buds except for one or two small areas where typical but minute clusters appeared. A report by Cramer and Horning⁵⁷ of prevention of the appearance of spontaneous mammary carcinoma in mice by a preparation containing the thyrotropic hormone of the anterior lobe of the pituitary gland led to the consideration of a possible inhibitory effect of the gonadotrophic substance in this case. The later development of typical carcinomas in 2 other relatively young mice led to the abandonment of any such theory for the hormone used.

⁵⁷ Cramer, W., and Horning, E. S. Prevention of Spontaneous Mammary Cancer in Mice by Thyrotropic Hormone of Pituitary, *Lancet* 1 72-76, 1938.



Fig 44—Typical precancerous clusters developing in a mouse of the "high tumor strain," aged 12 months, after 2,370 rat units of gonadotropic factor of the urine of pregnant women had been given. Gross preparation

It must be concluded, then, that this gonadotropic substance neither stimulated nor inhibited mammary proliferation in either of these strains. It might have been expected that an increase in estrogenic substance produced through stimulation of the animals' own ovaries would have affected the breasts. As a matter of fact, examination of the ovaries showed them also to have been little affected. It is possible that the long-continued injections led to the formation of antihormones which counteracted any other effect. Such an explanation is not, however, necessary, for when it is remembered that relatively large doses of estrogens did no more than accentuate proliferation of the mammary glands of the dilute brown strain and had little effect on the C57 strain, it is not surprising that the morphologic effect on the mammary glands of an indirectly produced estrogen should be unrecognizable.

TABLE 12—*Duration of Injections and Total Dose of Lactogenic Principle of Anterior Pituitary (Prolactin)*

Cancer Resistant Strain (C57)			Cancer Susceptible Strain (dba)		
Mouse Number	Injection Period in Days	Total Bird Units Injected	Mouse Number	Injection Period in Days	Total Bird Units Injected
82	29	42	58	44	76
89	32	48	57	64	110
88	65	112	28	93	160
72	65	112	68	113	194
04	130	228	25	124	204
40	134	234	81	124	204
18	271	378	31	107	246
14	271	468	37	274	432
84	313	528	30	290	474
83	347	588	29	302	522
21	379	630	22	309	522
58	429	718	15	317	522
29	388	750	21	438	7.6
30	338	750			

EFFECT OF LACTOGENIC PRINCIPLE OF ANTERIOR PITUITARY (PROLACTIN)

Prolactin (Squibb), divided at first into six and later into two doses, was injected to give a total weekly amount of 12 bird units. Fourteen animals of the C57 strain and 13 of the dilute brown strain were treated for periods ranging from one to fourteen months (table 12).

Cancer-Resistant Strain—The ducts of the C57 strain after injection of prolactin were often considerably dilated and contained more secretion than was normally encountered. There was also probably a little increase in the periductal collections of lymphocytes (fig 45) and in the connective tissue along the course of the ducts. The acini as a rule showed no increase over their normal number. In a rare case

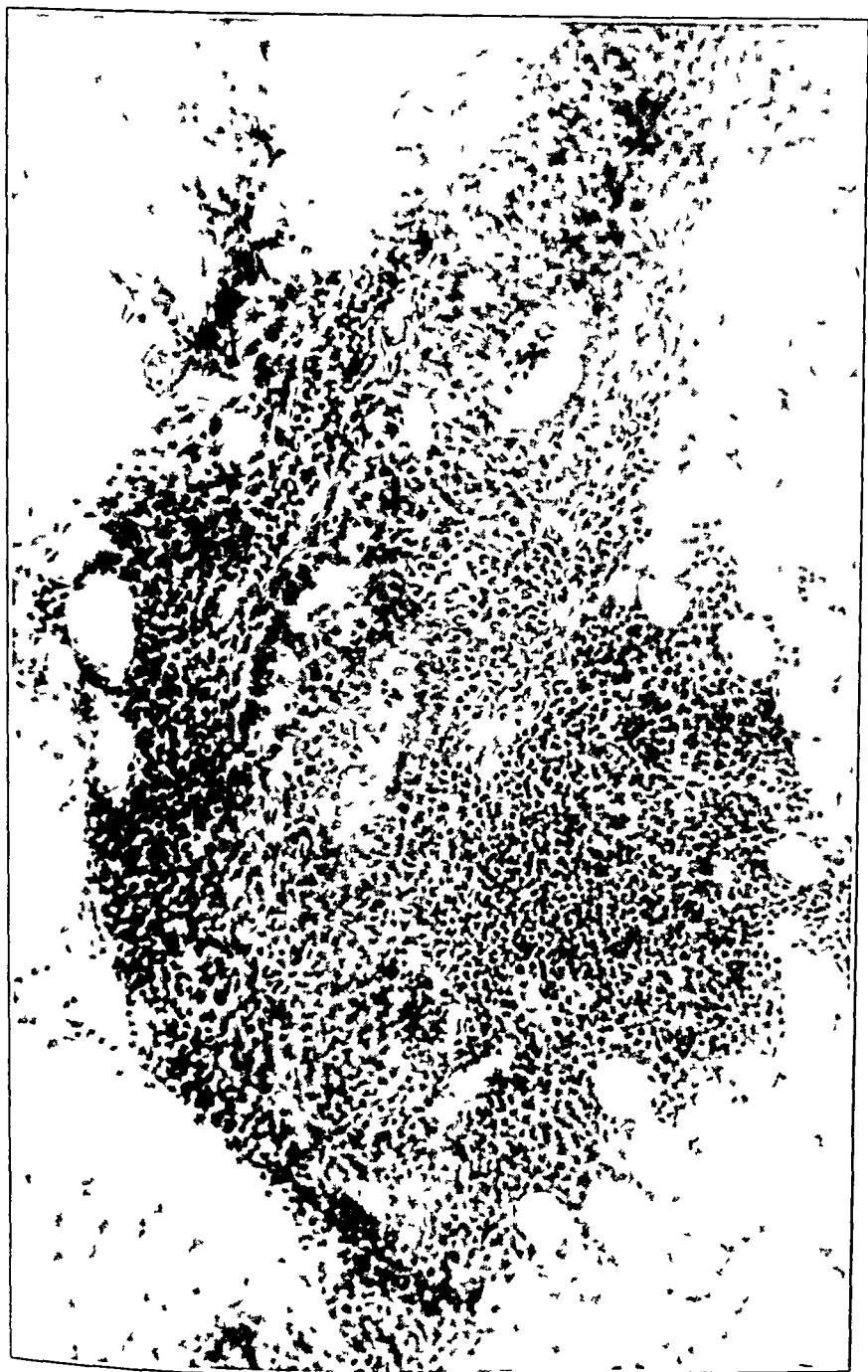


Fig 45—Lymphocytic collections along the duct in a mouse of the "low tumor strain" at the age of 6 months, after 234 bird units of prolactin had been given
Gross preparation

the possibility of some development of new acini could not be positively excluded, but the relatively large numbers of side branches noted in some preparations were probably within the limits of the normal variations of the strain. Evidences of increased secretion in either the cells or the lumens of acini were notably absent. The presence of many lymphocytes may have been an indication, however, of stasis of secretion in the ducts.

Cancer-Susceptible Strain—Positive findings to distinguish this group from the untreated animals of the same strain were also lacking. The ducts were as a rule much dilated but never showed any epithelial hyperplasia and contained only a little secretion in the prepared specimens. The acini, as in the normal animals of the strain, proliferated early, at first forming delicate feathery or tufted structures but later producing bulbous dilatations suggesting distention of the acini with secretion. Although precancerous clusters were not infrequent, the degree of acinar development varied greatly, and in the 3 oldest animals the acinar development was relatively slight.

Microscopic examination showed the characteristic clusters of acini observed in the normal animals of the strain and often markedly dilated ducts. The amount of secretion detectable in the sections did not approach that in the group treated with estradiol benzoate and perhaps did not exceed the normal. Collections of lymphocytes about the acini were again perhaps indirect evidence of stimulation of secretion by prolactin. Although there was some suggestion of a diminished acinar growth in these animals of the dba strain treated with prolactin, there is no basis to claim an inhibiting effect. Furthermore, palpable cancer developed once among the 6 animals which lived over ten months.

SUMMARY

The basic difference in the structure of the mammary gland of the two strains is persistent no matter what endocrine principle is injected. Thus, the mouse of the C57 strain receiving the largest amounts of estrone (theelin) or estradiol benzoate exhibited a far less complex mammary structure than did the untreated animal of the dilute brown strain. The importance of hereditary constitution as opposed to extraneous endocrine stimuli is thus strikingly emphasized.

The effect of estrone and of estradiol benzoate on the C57 strain was simply to cause moderate proliferation of the acini, while the action of these substances on the glands of the dilute brown strain was acceleration and intensification of their inherent tendency to acinar production. The lesion thus produced was adenosis with a marked tendency in one strain to become malignant. Morphologically it resembled the areas of acinar proliferation, adenosis or localized adenoma sometimes seen in human chronic cystic mastitis (fig 4).

Hyperplasia of the lining of the ducts was not prominent in these treated mice. In some animals, especially of the dba series treated with estradiol there was evidence of some reduplication of the epithelial lining of the ducts. These changes were associated with secretion in the ducts and the appearance of new connective tissue, lymphocytes and fat-containing endothelial leukocytes in the periductal tissues. The lesion thus produced somewhat resembled periductal inflammation in women with abnormal secretion from the nipple (figs 5 and 6), but complex hyperplastic lesions, such as papillomas or complete filling of the ducts by epithelium (fig 8), were entirely missing.

Gonadotropic substance from the urine of pregnant women had no effect on the epithelium of the mammary glands of either strain. It could not be demonstrated that it either accelerated or retarded the formation of carcinoma.

Lactogenic substance also had no effect on the proliferation of epithelium. In certain animals, especially of the C57 strain, there were some dilatation of the ducts and slight signs of secretion in the ducts.

The other characteristics of human chronic cystic mastitis were little in evidence.

Definite connective tissue proliferation appeared in a few mice, always about the ducts, and was probably to be explained on the basis of a reaction to chronic inflammation. The histologic picture of the common type of human mammary disease in which connective tissue proliferation leads to diffuse adenofibrosis was not reproduced by this means (figs 1 and 2).

Cysts never occurred. The gross preparations proved beyond question that the large, epithelium-lined structures encountered microscopically were simply cross sections of dilated ducts.

"Pale epithelium" comparable to that so frequently encountered in the human disease was never observed in these preparations.

On account of basic anatomic differences between the human and the mouse mammary glands it cannot, perhaps, be expected that morphologically identical lesions should occur. Nevertheless, the contrasts in appearance of estrogen-produced mammary lesions in mice and the spontaneous lesions of so-called "chronic mastitis" in women may well be the result of differences in etiology as well. Certainly discrimination should be exercised in using evidence derived from the study of artificially produced epithelial hyperplasia in mice to explain benign mammary proliferation in women.

CONCLUSIONS

- 1 The characteristic lesion arising spontaneously in the mammary gland of mice susceptible to carcinoma and that produced by estrogenic

substances is a diffuse adenomatous proliferation of acini. Morphologically similar structures are sometimes seen in human mammary disease, but their presence does not constitute an essential feature of "chronic mastitis."

2 The diffuse fibrosis or adenofibrosis which is characteristic of the commonest form of benign mammary disease in women has no morphologic counterpart in the lesions of the mammary glands of mice, whether spontaneous or induced by administration of endocrine substances.

3 The human disease characterized by retained secretion in dilated ducts, moderate hyperplasia of the lining of the ducts and signs of periductal inflammation is rather closely imitated by lesions in mice developing after prolonged administration of endocrine substances, especially of estradiol.

4 Complex neoplastic lesions of the lining of the ducts occurring in the human breast, such as papillomas or proliferation of the epithelium to fill the ducts completely, do not develop in the breast of the mouse either spontaneously or after prolonged administration of estrogens.

CORRECTION

In the article by Dr. Gordon Murray entitled "Heparin in Surgical Treatment of Blood Vessels," in the February issue (*ARCH. SURG.* 40:307, 1940) the name "Labey" should be substituted for "Key" in the second line on page 312, and footnote 4 should begin "Labey, cited by Key."

COMPOUND FRACTURES

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A compound fracture is a broken bone with an associated wound of the overlying skin. Even if the wound does not actually communicate with the fracture line, the intervening tissue barrier may be insufficient to prevent spread of infection.

PATHOLOGIC PICTURE

It makes little difference whether the wound of the skin is caused by protrusion of the bone fragment from within or by the force from without. The tissue is potentially infected in either case. The prognosis and thoroughness of treatment are influenced greatly by the conditions under which the wound was received. The prevalence of the more severe pathogenic organisms is greater in manured fields, horse-inhabited streets and stables, shell-torn country and dirty clothes than it is in the woods, in steel mills or in clean houses. Uninjured, clean clothing and careful protection in transportation are comforting incidents. The severity and extent of the damage to the soft parts are important factors. The element which determines success or failure most of all is the interval which elapses between the original injury and the institution of proper treatment. Every quarter-hour counts in getting rid of the invading organism and devitalized tissue.

TREATMENT

General Principles—The objects of treatment are threefold: (a) to care for the general condition of the patient, (b) to obtain healing of the broken bone with the best possible alinement of the fragments and the least possible impairment of function, and (c) to prevent or control infection.

(a) Patients with compound fractures often have multiple injuries and show varying degrees of shock. Treatment of the latter should be instituted immediately, but only with pulseless, moribund patients should treatment of shock be allowed to delay operative procedures beyond the time required for obtaining necessary roentgen evidence and preparation.

of the operating room Treatment of shock is continued in the operating room while other surgical measures are being carried out

(b) The principles of treatment of the bone are the same for compound as for closed fractures

- 1 Minimize the secondary trauma of transportation and examination
- 2 Reduce displacements early and accurately
- 3 Immobilize sufficiently the broken bone
- 4 Mobilize early the adjacent joints and muscles
- 5 Maintain local circulation at its optimum

(c) The principles of prevention or control of infection are as follows

- 1 Protect the wound and immobilize the injured part before transportation
- 2 At the earliest possible moment, surgically remove all foreign material and devitalized tissue
- 3 Avoid tension in the wound
- 4 Provide rest for the injured part
- 5 Administer serums and drugs to combat organisms

Details of Treatment—1 Shock If the injured part has not been splinted properly before the patient arrives at the hospital, this should be done before he is moved from the transporting vehicle Morphine should be given immediately to reduce pain and lessen muscular spasm Rest and heat may be all that is necessary while roentgen and other examinations are made, but if the pulse, pressure and hematocrit readings indicate it saline solution, dextrose or blood should be given first Unless the symptoms of shock are marked, administration of these substances can be carried out during the operative procedures The best way to lessen shock is to get the debridement and immobilization done as soon as possible

2 Chemotherapy Antitetanic serum should always be given If gas-forming organisms are suspected, prophylactic serums may be included The use of sulfanilamide and the related drugs as a routine procedure is still debatable In some clinics sulfanilamide is now used either locally or generally In view of the complications and sequelae our plan is to use it only when smears or cultures after debridement yield bacteria

3 Debridement This term has been universally adopted to describe operative removal from a wound of contaminating foreign material and devitalized tissue The success of the procedure will depend on the time at which it is done and on the thoroughness and gentleness with which it is carried out If it is done within a few hours of the accident one may hope to remove most of the contaminating material After

twelve hours the best one can do is to control the existing infection. After the patient is anesthetized, the wound should be protected with sterile gauze while the adjacent skin is thoroughly shaved and cleaned. The wound itself and any exposed tissue should be gently washed with saline solution, care being taken not to allow the fluid to enter the deeper planes. A strip of skin 0.5 cm wide is then dissected from the margin of the wound, and the wound is enlarged sufficiently to allow free exposure of the deeper portions. The skin is covered by towels attached to the edges of the wound. With fresh instruments each layer is then carefully attacked until the whole area has been explored. In removing the foreign material and devitalized tissue great care must be observed not to drive the contamination into the depths of the wound. It is unwise, therefore, to restore the structures to their normal position before they and their bed have been thoroughly cleaned. For this reason the practice of reducing compound fractures and carrying out the debridement through a hole in the encasing plaster is to be condemned. In irrigating the wound, large quantities of saline solution should be used. The stream should be made to flow from the depths of the wound outward, with good retraction. If the irrigating can is held high and the nozzle placed in a small wound, the infection can be carried long distances along fascial planes. It is unwise to use any chemicals stronger than saline solution on the raw tissues. It seems foolish to try to remove tissue devitalized by the trauma and then to sear the raw surface by strong chemicals. These may kill some pathogenic organisms, but they also kill human cells.

4 Reduction of Displacements. The plan of controlling the infection first and reducing the fragments later has resulted in many deformities and disabilities. The time for reduction is as soon as the debriding operation has been completed. If this can be accomplished and the reduction maintained the patient will at least have a straight limb of the proper length.

5 Immobilization. Rigid fixation is even more desirable for compound fractures than for simple ones. It not only favors bone repair but helps to control the infection. Frequent movements of the ends of the bone, even through a small arc, tend to tear the limiting wall of granulation tissue and let the infecting organisms invade new tissue. Plaster encasements may be sufficient for transverse fractures without comminution. Openings must be made sufficient to allow dressing of the wound.

For oblique or comminuted fractures single wire traction with suspension in a plaster gutter splint may be used. Some prefer to insert wires above and below the site of fracture and to embed these in a circular plaster splint.

For a number of years I have used internal metal fixation. At first the screws or the plate and screws were applied through an incision separate from the original wound. In recent years, however, they have been inserted through the original incision. The leg or arm is then suspended in a plaster gutter. This method allows whatever treatment of the wound seems desirable, permits mobilization of adjacent joints, avoids constriction of circulation and insures proper length and axis. The hardware usually is removed after it has served its purpose.

6 Treatment of the Wound. The ideal method is to carry out the debridement so early and so thoroughly as to avoid infection, so that the wound may be sutured primarily. Usually, however, some infection is left behind, and if there is tension in the wound it is much more apt to spread and do serious damage than if the secretions find a ready exit. Primary suture is being successfully carried out in many clinics, but the incidence of serious infection, extensive osteomyelitis, amputation and death is higher than when the wounds are left open, at least for a while. Secondary suture or healing by granulation with subsequent skin grafting is safer.

The problem of deciding what is the best subsequent treatment of the operative wound is an interesting one. It is undoubtedly true that frequent, rough dressings with careless technic do more harm than good. It is also admitted that the normal efforts of the body tissues and fluids to resist the invading organisms are of great value. These should be helped and not hindered. Wide experience has shown that the Carrel method does control infection and help to get rid of devitalized tissue. It is my opinion that for compound fractures which can be debrided and immobilized properly within eight hours of the injury and in which the local damage to tissue is not too great, it is better to separate the surfaces of the wound with petrolatum gauze with no tension in the wound and to change the dressings infrequently. When the debridement has been delayed or incompletely carried out it is wiser to use the Carrel method.

CONCLUSIONS

Treatment of compound fractures involves healing of the broken bone and of the injuries to the soft parts and control of infection. The future course depends largely on the character of the original injury, the amount of secondary trauma incident to transportation, the thoroughness of the primary treatment of the wound and the time at which it is carried out. With early debridement, efficient reduction and firm immobilization the type of subsequent treatment of the wound becomes of less importance.

TREATMENT OF COMPOUND FRACTURES

WITH SPECIAL REFERENCE TO MILITARY SURGICAL PROCEDURES

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Traction, reduction, drainage, debridement, wound sterilization and immobilization are terms used in thousands of pages that have been written about the contributions of the great war to civil surgery. Yet these very terms constitute some of the difficulties in dealing with the subject under consideration, for many papers and even textbooks have left the reader in doubt as to their exact meaning. And, too, meanings change as ideas develop. Claims for the so-called new methods and effects of war methods on civil practice underwent considerable change after the war, up to the publication of the Surgeon General's report in 1925.

Overseas experience during the war years revealed to me not only confusion of terms but an unfortunate confusion in principles and in practice. To surgeons with what Sir Robert Jones called an "orthopedic conscience," many methods and technics prevailing during the war were far from satisfactory. It was the practice to treat compound fractures as wounds until healed and then as fractures. Splinting was a compromise in most cases, adapted so that the Carrel-Dakin or some other antiseptic treatment of the wound could be carried out. Prolonged delay in healing of the fracture, as well as deformity and disability, was the result, as hundreds of cases that came under my personal observation testified. There was a surprising return to the mobilization methods of Championniere, even septic joints were kept moving, and disastrous local and general infections resulted. Infected wounds presumably rendered sterile by chemicals were sutured. True, there were a few brilliant primary or secondary closures, but there were also many "explosions." The principle of drainage for infection was forgotten in these attempts to cover up pockets of active or latent septic organisms.

Some of these methods and technics were proposed as new principles. Yet actually most of them violated or disregarded such fundamental principles as immediate reduction of fractures, drainage for infected wounds, immobilization in correct position and control during repair of the fracture. Restoration of circulation and nerve supply and provision for rest to favor physiologic function in injured and inflamed parts were neglected. Apparently it was forgotten that these are absolutely essential for defense against infection and for repair.

Such were the considerations that led me to search for a better program for the treatment of compound fractures in the years just after my military experience from 1917 to 1919. I began with a different method of treatment of osteomyelitis and other infected wounds and in 1923 published an account of the method and results up to that time. The plan was designed to conform to the real fundamentals of fracture treatment. I carried out immediate reduction and instituted and maintained adequate drainage for all compound fracture wounds. For primary traction and permanent fixation I employed plaster of paris with moleskin adhesive plaster, ice tongs or pins. Finally, I protected the wound against trauma and secondary infection during the operative treatment and after-care by avoiding postoperative dressings. This was tried out first in cases of chronic low grade infection, but it was soon found that the patient could defend himself against almost any kind of infection if the surgeon would refrain from the usual custom of traumatizing the surface of the wound and adding new and different organisms by exposure, dressings, instruments and fingers every day.

The program I proposed in 1923 was as follows:

1 Prior to any operation in a case of chronic osteomyelitis or of compound fracture, immobilize the patient on a traction table with all of the injured parts as nearly as possible in correct anatomic position (fig 1). Reduce the fractures at once, especially by efficient traction, so that circulation and nerve supply are restored. If there is older deformity, correct it first by traction and manipulation. Even in seriously injured patients with multiple fractures or extensive injuries to the thigh, shock may nearly always be avoided by preliminary control of the patient in this way. If a patient arrives at the hospital in shock, employ the customary medication—intravenous dextrose solution, physiologic solution of sodium chloride given hypodermically or blood transfusion. But do not leave him with a mangled limb unreduced and tortured by painful movements and muscle spasm. Efforts to relieve shock (shock therapy) are often futile if the local conditions that cause so much suffering are not relieved.

2 Open the entire infected area and drain by a suitable operation (debridement), so that foreign material and dead or dying tissue are removed. As part of the drainage operation the wound may be wiped out with pure tincture of iodine and alcohol, as in preparation of the skin, in order to reduce the amount and virulence of the accidental infection.

3 To protect the surface of the wound and provide permanent drainage, fill the wound with a nonabsorbent, nonirritating petrolatum pack. (This is the open wound treatment that has prevented gas

bacillus infection and tetanus in so many cases) Use no drainage tubes, and do not cover any parts of the wound by flaps, sutures or overhanging portions of tissue The pack must be carried to the depths of the wound, and it must flow over the edges at the top to a distance of about 1 inch (2.5 cm) on the surrounding skin This is to carry dis-

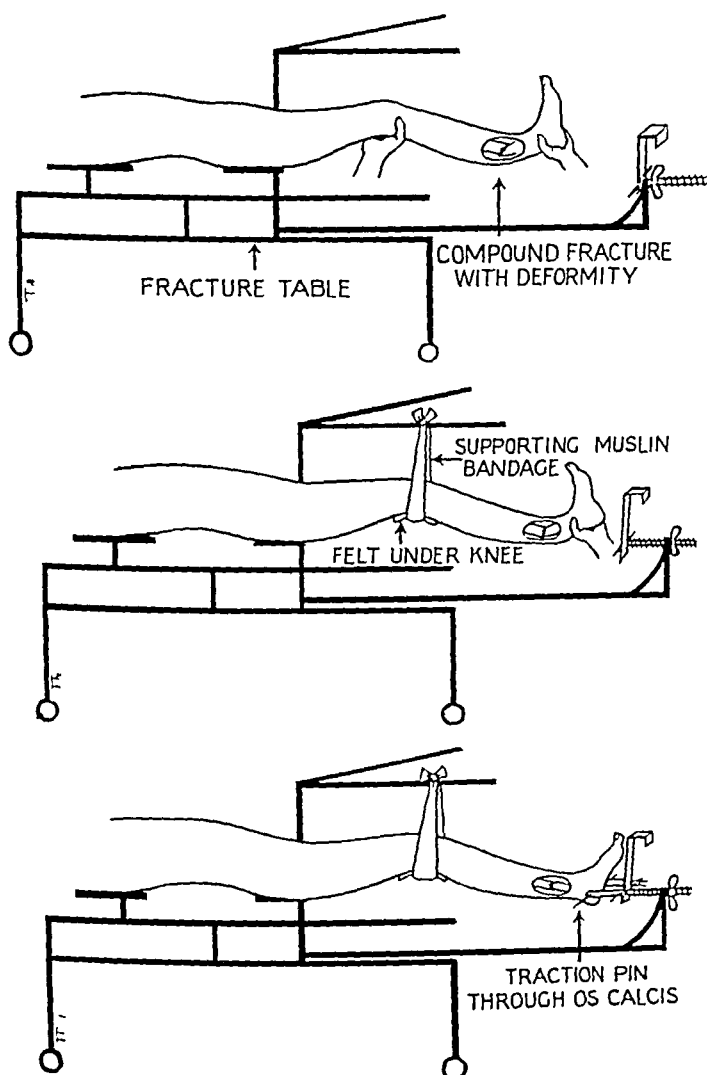


Fig 1—Initial stages in the treatment of compound fracture

charges away from the area just around the wound Complete the dressing with a dry, sterile absorbent pad bandaged firmly over the drainage pack and its edges

4 Enclose the entire limb in a plaster of paris cast In cases of fracture and after the correction of deformities, incorporate in the cast the moleskin adhesive plaster, ice tongs, traction pins or pins extending

directly into the fracture fragments (fig 2) This makes permanent the traction and fixation obtained on the table during operation Casts must fit well and be sufficiently extensive to overcome once and for all muscle spasm and irritative motion of all kinds

5 When removal of a severely injured limb is indicated or even definitely impending, wait, if necessary, for improvement in the patient's local or general condition But lest this waiting be unprofitable, relieve pain, shock and infection by immobilization of the limb in correct

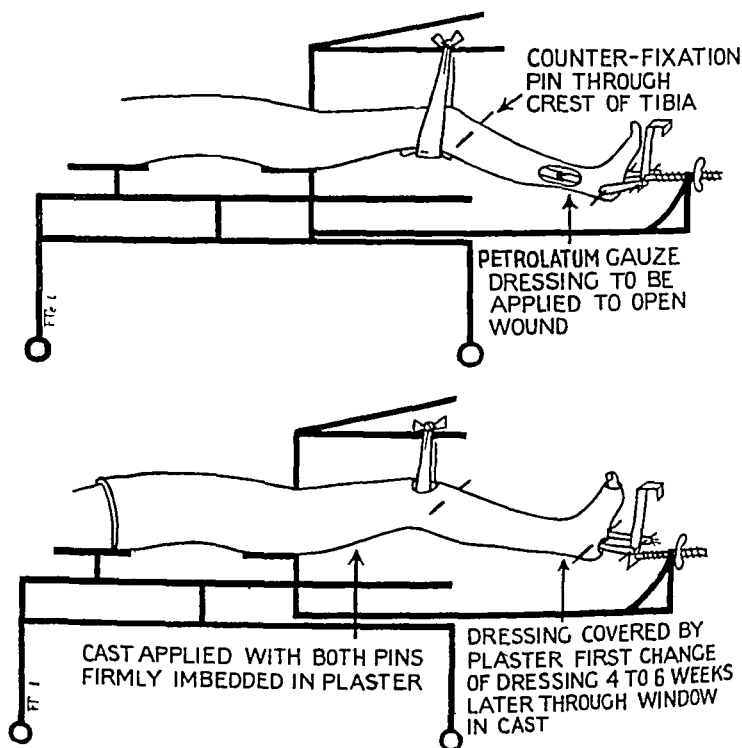


Fig 2—Further stages in the treatment of compound fracture

position and by adequate drainage while other supporting measures are employed

6 Finally, do no postoperative dressings If immobilizing devices become inefficient, if discharge is profuse or if odor (because of mixed infection) becomes unendurable, change dressings in the operating room without disturbing the parts and with a minimum of damage to the surface of the wound Usually the original dressing may remain in place for four to eight weeks or even longer, until the wound has made good progress toward healing

If such a program is to be adhered to a number of misconceptions must be laid aside

1 The misconception that "primary treatment must be delayed to allow the patient to recover from shock," hemorrhage or swelling. The fact is that all of these conditions may be prevented or relieved by immediate reduction and control of the injured parts in correct length and position. With reduction of the fracture there is restoration of circulation and nerve supply, hence all of the physiologic functions in the injured part may be expected to improve.

2 The misconception that "every injury is an individual problem to be solved by the particular surgeon attending in each case." This is a general teaching which has done much harm. Adherence to a routine calling for reduction of the fracture and control of the limb will soon convince any surgeon that there are certain rules that are applicable to every case, regardless of time, place or circumstances.

3 The misconception that "plaster of paris cannot be used in the treatment of fractures" because it implies constriction of the limb and will do harm by interfering with circulation. No properly applied plaster of paris cast is tight enough to cause constriction or distress. A painful cast is an improperly applied cast. When a cast including fixation pins has been applied immobilization in correct length and position is "un fait accompli." On modern traction tables, reduction of the fracture, suitable drainage dressings and a correct plaster of paris dressing with skeletal fixation may all be effected quickly, without difficulty or delay.

4 The misconception that "infection must be combated by active chemical antiseptics" and therefore that splints must be adjustable or removable. It is too often forgotten that Lord Lister, when he introduced the antiseptic method, placed his chief reliance on exclusion of infection from the wound and on the patient's resistance to overcome local and systemic infections. Lister advised repeatedly against the application of phenol and other chemicals directly to the surface of the wound. He warned also against the introduction of infection at the time of dressings and the distribution of infection by metastasis. Frequent dressing, by whatever method, violates the principle of protecting the surface of the wound and the patient against secondary infection. Even such a method as the introduction of maggots every few days subjects the patient to greater risk of mixed infection than does an irrigation or an antiseptic dressing.

5 The misconception that "the wound must be kept clean." As long ago as the time of Ambroise Pare and John Hunter mechanical cleanliness of the wound was shown to be unnecessary. It is specific infection and particularly mixed infection that does the damage in these cases. If the patient can have his original damage and infection minimized by an adequate primary surgical procedure and if he can then be protected

against irritation from movement, muscle spasm and frequent dressings, he will usually be able to defend himself. This is true especially if correct anatomic relations and physiologic function have been restored to the injured extremity.

6 The misconception that "fractures cannot be reduced secondarily or deformity corrected in the presence of infected wounds." During my military service with the British twenty years ago, I was taught that compound fractures must be soundly healed for several months before any surgical procedures could be attempted. Procedures to correct fracture deformities or nonunion and even operations on the peripheral nerves had to wait, not only until healing had been obtained (often it never was obtained) but until the scarred region would withstand a period of massage without "lighting up." Now it is known that under the conditions I have described, that is, drainage when necessary, anatomic reposition, perfect immobilization and protection against infection both at operation and afterward, any of these operations may be done at any time. To do such operations without delay is especially important when control of a fracture has been lost or when deformity is impending or has occurred. In this way long periods of disability and deformity are prevented. Moreover, many patients will heal early, with good limbs, who would go through much longer periods of healing if their deformities and other pathologic conditions remain unrelieved.

My suggestions, including more or less fixed rules for early reduction and the use of closed plaster of paris casts with no opportunity for inspection of the wounds, have aroused some opposition. In some cases the casts became soiled and because of mixed infection had a bad odor.

The use of my methods for military operations was suggested to the Surgeon-General's office almost twenty years ago. At that time their adoption could not be brought about because the plan of treatment was "too much out of line with usual practice."

The years have piled up evidence that the program proposed twenty years ago was sound. I now have documents to show a remarkable success of the method in the military hospitals in and around Barcelona during the Spanish civil war. Trueta¹ reported that in the entire area of which he was director more than 10,000 patients were treated by primary reduction, plaster of paris casts and infrequent dressings. His reports show that the patients treated early in this way were more com-

¹ Trueta, J. *Treatment of War Wounds and Fractures with Special Reference to the Closed Method as Used in the War in Spain*, London, H. Hamilton, 1939. Dr. Trueta has generously recorded his indebtedness for the methods he used. "In concluding this book, I wish to offer my tribute to Winnett Orr, the advocate of a therapeutic method which is bound to give new direction to surgical practice in its attempt to aid the resistance of the body to infection. He taught surgeons once again to realize that rest is the complement of surgery."

fortable and that they escaped the early septicemias, tetanus and other anaerobic conditions to which such patients with sutured wounds and poorly splinted limbs are subject. He has pointed out also that they endured transportation well and that they recovered sooner and with better limbs. Trueta's¹ personal experience is indicated in table 1.

In commenting on this large and unusual experience, he said

I sincerely believe that no other treatment could have enabled us to alleviate for so many victims the horrors of war and air raids. The experience recorded covers thirty months' continuous treatment of war casualties, including the immediate surgical treatment of casualties in 300 air raids. By rapid, properly planned, boldly executed surgery, followed by closed plaster-of-paris casts, the casualties of war can today be spared the torment of having to pass the rest of their days

TABLE 1*—*Results of Treatment of Open Fractures by the Methods Described*

Type of Fracture	Cases	Good or Satisfactory Results	Bad Results	Deaths
Scapulohumeral	55	55	0	0
Shaft of humerus	142	140	1	1
Elbow joint region	64	60	4	0
Forearm	121	110	11	0
Wrist and hand	106	93	13	0
Hip and neck of femur	21	17	2	2
Shaft of femur	101	88	12	1
Knee joint	43	40	3	0
Shaft of tibia and fibula	225	193	25	2
Ankle and hindfoot	67	60	7	0
Forefoot	128	115	13	0
Total	1,073	976	91	6

* Quoted from Trueta,¹ p. 135.

crippled and mutilated. I believe that this is especially true of the victims of air raids if the surgeon is prepared to work in or close to the bombarded area. To the possibility of working under the strain of repeated aerial bombardments my colleagues in Barcelona and I can testify.

Trueta's figures show better results for such injuries than any previously reported in civil or military practice. One can see that his patients were protected by this plan against the advanced septicemia so often seen in patients when they arrive at the hospital. His experience in the prophylaxis of gas bacillus infections assures me once more that the plan of leaving wounds open is a factor of importance in dealing with all the anaerobic infections. That the petrolatum pack and the cast exclude oxygen from these wounds is, of course, an erroneous idea.

The principle of primary reduction and immobilization in correct position is readily accepted. But if it is proposed to carry out this program by manual reduction and application of ordinary splints only, the experienced and expert surgeon can succeed with the method. Tech-

nics such as delaying of reduction to await subsidence of swelling, suturing of wounds with tube drainage, use of wire splints or split casts, and weight and pulley traction with only sand bags or pillows for splints (all unfortunately still common), are, to say the least, inadequate

The points for consideration in both civil and military practice are as simple as they are important. For first aid on the battlefield or at the scene of the accident the use of a tourniquet and traction immobilization in a Thomas splint have demonstrated their value as life-saving and limb-saving expedients. Prepared in this way, the patient may be transported safely to a hospital where more efficient traction, debridement, petrolatum pack drainage and fixation in a plaster of paris cast may all be done. This is the plan that I have followed for many years, that is now being employed by many hundreds of surgeons and that was followed so successfully by Trueta at Barcelona.

The same technic is to be applied whether the treatment is primary, that is, applied during the first few hours, or secondary, in the sense that the patient arrives with the fracture in malposition, the wound infected and septicemia and pyemia already established. A restless patient with an unreduced fracture, muscle spasm, pain and a septic wound can do himself far more harm every hour than the surgeon will do by a thirty minute maneuver after which the compound fractured limb will be permanently immobilized in correct position, the wound adequately drained and the surface of the wound and the limb fully protected against further trauma and infection.

Illustrative of the principles and technic we advocate is the following report of a case.

REPORT OF A CASE

D. L. T., a youth aged 19, of Lincoln, Neb., was shot through the right leg while running away from an officer. He sustained a compound, comminuted fracture of both bones just above the ankle (fig. 3A). He came to me twenty-four hours after his injury with the leg in a foot and leg splint. There were considerable deformity and extensive comminution, the wound of entrance was small, but the wound in the front of the leg was large, and a large, loose fragment of tibia was lying with a point protruding when the dressings were taken off. The hemorrhage had been severe and recurred on removal of the dressing.

A traction pin was put through the calcaneum, and the leg was pulled down at once to full length. The leg was lined up as to the foot and knee without much reference to the fracture fragments at first. A second pin was put through the tibia a few inches above the fracture area. The position of this pin is indicated in figure 3B. The exit wound was enlarged slightly, and the large fragment of tibia, which was entirely separated from all tissue attachments, was taken out. Some search of the entire wound area was made for other bone fragments, a few of which were removed, and for particles of clothing that might have been carried in. A considerable number of clots were evacuated. This wound was not packed to the bottom. It was felt that there was a good prospect of rapid healing without extensive packing of the wound. A petrolatum pack was put over the point of

entrance of the bullet, and a partial pack was made of the wound in front with the petrolatum pack extending out over the edges of the wound onto the skin. Iodine was used to clean the entire limb above and below the region of fracture prior to any exploration, but no antiseptic was used inside the wound cavity. There was no established infection, although the patient had a temperature of 100 F on his admission to the hospital, and this temperature continued to rise slightly for several days. By the fifth day, however, the boy's temperature was normal, and it remained so.

The cast and dressing applied on January 25 were not disturbed until March 9. At that time the cast was removed, the pins were taken out and the wound was dressed. The wound of entrance was healed, the wound of exit in the front of the leg was still slightly open, but there was no inflammation, swelling or

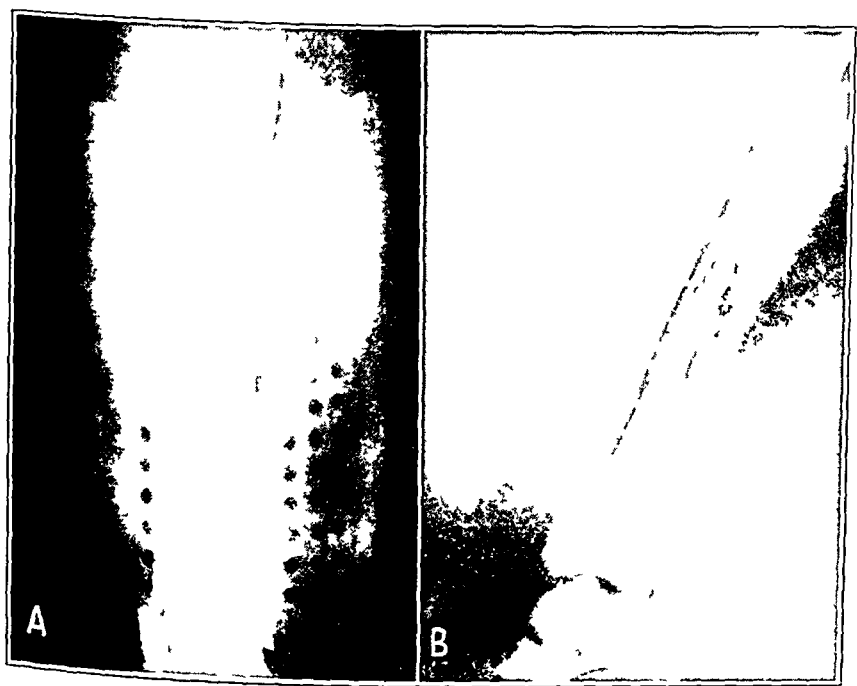


Fig 3—A, compound fracture of both bones just above the ankle. B, position immediately after pin traction and debridement.

evidence of septic complications. The limb was in satisfactory position. A very slight change as to rotation and dorsiflexion of the foot was made without disturbing the fracture area. A new cast was applied above the knee, without pins or fixation otherwise, and this cast was worn for another period of six weeks.

During the second six week period the boy got about a good deal on crutches and, contrary to my instructions, bore some weight on the limb. On removal of the second cast, on April 24, all the wounds were healed and the fracture was firmly consolidated, but because of the weakness of the tibia (indicated in figure 4 B), a double lateral walking iron was put on below the knee. This was worn until May 20.

The treatment of this patient is described as typical of the kind of treatment that all these patients may have. It is my belief that with less adequate fixation methods and frequent dressings he would have pursued the usual course of a patient with a

compound infected fracture, with all the signs of local and general infection, to which such patients are subject

Photographs of the limb as of Dec 30, 1939, eleven months after the original injury, are presented to indicate the kind of recovery obtained by this very simple treatment (fig 4 B)

Trueta's figures are the latest and best statistical results that have been brought to my attention. Many others, however, have made reports indicating a high percentage of recovery in cases of compound fracture and chronic osteomyelitis treated by infrequent dressing



Fig 4—A, roentgenograms showing defect of the tibia. B, roentgenograms taken eleven months after the original injury.

In 1931, Kulowski, then at the Steindler Clinic in Iowa City, made a statistical study of results in cases of chronic osteomyelitis, including compound fractures, from the clinics of Burns at Madison, Wis, Gaenslen at Milwaukee, Steindler and Kulowski at Iowa City and Orr and Thomson at Lincoln, Neb. There were 426 cases, with 358 instances of healing (84 per cent). All of these were treated by the methods described in the present paper. As an interesting comparison, the results of the Baer maggot method at that time showed healing

in 45 per cent of cases (according to the posthumous report of Baer,² the final arrangement of which was completed after his death by his associate Dr George E Bennett)

During 1932 I made a report on all of my compound fractures up to that time. Of 85 infected fractures, 76, or 90 per cent, were healed,



Fig 5—Photographs of the patient whose fracture is shown in figures 3 and 4. These photographs were taken one year after injury.

of 183 fractures compounded by operation for deformities and disabilities of various kinds, 100 per cent were healed without infection.

² Baer, W. S. Treatment of Chronic Osteomyelitis with Maggot (Larva of Blow Fly). I. Bone & Joint Surg. 13: 438-475 (July) 1931.

or failure of union in any case. For compound fractures of all kinds at that time, including those treated by my associate, Dr. Thomson, 268 in all, the results were as follows: Two hundred and fifty-nine were healed, 1 was not healed, 5 amputations were performed, and 3 patients died. The last-cited figures included 84 fractures and fracture infections treated at the Veterans Hospital in Lincoln. Many of these dated from the war days of 1917 and 1918. There were 84 of these, 54 of the patients came to the hospital with unhealed or malunited fractures. Of the 84, 79, or over 90 per cent, entirely recovered.

In 1933, I reported the following cases for one year to the British Medical Association:

There were 6 primary compound fractures, with a total of seven dressings and an average healing time of ten weeks. In the 25 cases in

TABLE 2—*Summary of Cases and Results*

Dr. Orr Only	Compound Fractures			Good Results and Healing	Poor Results	Results Unknown	Deaths	Total
	Primary	Secondary	Compounded by Operation					
1921 to 1929 (published in Detroit lecture, 1930)	60	98		158	1	0	0	158
1929 to 1933 (not published)	86	58	61	187	6	9	3	200
1934 to 1938	6	75	75	131	7	0	2	156
Femurs only, to 1938	14	50	75	127	5	5	2	139
Total	166	281	211	603	19	30	7	658

There is some overlap in cases of fracture of the femur from 1921 to 1933, but such cases are not included in the figures for 1934 to 1938. "Compounded by operation" includes all plastic operations for correction of malunited fractures and leg lengthening operations.

which secondary operations for compound fracture were done, the average duration of preceding deformity, disability or chronic osteomyelitis or all three was eight months. The fractures all healed, with an average for the 25 cases of three dressings and three months' time for healing.

In 1934 I made a study of 1,300 patients with fracture treated in the city of Lincoln during the years from 1929 to 1933. I had done operations on 212 of these patients. Most of the operations became necessary because of unusual difficulties during or after the primary treatment. Removal of plates or wire or operation for nonunion or infection was necessary in 110 cases. In this series good results were obtained in 96 cases, or approximately 90 per cent. The defect in primary treatment in most of these cases was usually insufficient traction at first or failure to maintain traction in the after-care.

Table 2 is a recapitulation and summary of the various groups of cases referred to. Recent patients, many of whom are well, have not yet been included.

CONCLUSIONS

1 The method of immediate reduction, open drainage, plaster of paris skeletal fixation and infrequent dressing is one which is simple of application either for emergency patients or as a program for secondary surgical care

2 Reduction of a fracture depends on traction more than on any other factor. Sufficient traction can and should be applied at the time of operation, whether the operation is primary or secondary. Length and position should be maintained by skeletal pins fixed in the plaster of paris cast

3 Infected wounds at any stage should be left open, not sutured, with the surfaces of the wound protected against trauma and secondary infection

4 Fracture deformities may be corrected at any stage, even in the presence of local or general infection, if the aforementioned points are observed. All the injured parts are to be restored to correct position, infected wounds all left open, permanent immobilization in correct position maintained and the wound and the injured limb protected against further trauma and secondary infection

5 The experience of other competent observers, as well as my own, is that good results may be obtained by the infrequent dressing method in 85 to 90 per cent of compound infected fractures of all kinds

This experience has now been confirmed for military practice in Spain by Trueta,¹ whose observation of more than 1,000 cases in which similar treatment was given yields exactly the same percentage

TREATMENT OF COMPOUND FRACTURES

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First aid should be directed immediately toward reduction of the fracture by traction, protection of the wound with sterile gauze and splinting with plaster, steel or wooden splints

On the patient's admission to the hospital, anteroposterior and lateral roentgenograms are made

OPERATION

Sterile gauze is placed in the wound, the surrounding skin is shaved and thoroughly cleansed with soap, water, ether or benzine. The gauze is then removed from the wound, and an adequate debridement of the devitalized skin, fascia, muscle and detached bone is made. The debridement is of the greatest importance and should be done thoroughly. Wounds compounded from within are usually not as severe as those received from without, nor is the contamination as great. The fracture is then reduced and immobilized by splinting, and the Carrel method of treatment of the wound is instituted at once.

REDUCTION OF FRACTURE

Manipulation and manual traction should be attempted with external fixation, preferably plaster. If internal fixation with plates and screws is used a Thomas, Jones or Cabot splint gives complete satisfaction in selected cases. Molded plaster casts rather than circular casts should be used unless the latter are split within twelve hours, because of the possibility of complications due to constriction or gangrene. Repeated inspections should be made, and at the first sign of circulatory disturbance the splints should be released.

Should the reduction not be satisfactory an open reduction can be done after the local swelling has subsided and the temperature and pulse have become normal, which is usually at the end of ten or twelve days. The operative incision for fixation of the fracture with plate or screw is made not at the site of the original compound wound but at a point opposite, so as not to contaminate this particular field with the operative incision. The compound wound is permitted to granulate and is usually cicatrized before bony union has taken place. However, should a small sinus persist the plates and screws are removed and the wound closed.

WOUNDS COMPOUNDED FROM WITHOUT

Wounds compounded from without should be treated as potentially infected, a thorough debridement being performed at the earliest possible moment. The wound should remain open, and Carrel tubes should be inserted to every cavity and recess. Immediately after the operation the wound should be copiously irrigated through Carrel tubes with solution of sodium hypochlorite. At the end of two or three days the dressings are changed and new tubes inserted.

FIXATION OF FRACTURES WITH METAL

For the past thirty years I have used steel fixation routinely wherever indicated. Steel plates and screws are usually employed for transverse fractures and transfixion screws for spiral and oblique fractures. In selected cases, extensive comminuted fractures can be treated by bridging the site of fracture with long plates. Skeletal traction with Kirschner wires incorporated in the plaster is used occasionally but not as a routine procedure, because the introduction of pins or wires above and below the site of fracture increases the possibility of complications arising from the use of this technic. When indicated it is a perfectly justifiable procedure, but it should not become the method of choice to the exclusion of other recognized procedures. Extensively comminuted fractures do not usually lend themselves to fixation by screws and plates and should be treated by skeletal traction, preferably by Kirschner wire. If reasonable reduction can be secured with plates, traction by Kirschner wire is not necessary.

It is the general consensus that metal plates and screws are contraindicated in the treatment of compound fractures. Unless debridement and the Carrel wound sterilization are done thoroughly, plates and screws should not be used, as they tend to complicate the massive osteomyelitis which frequently results from infection. As a rule, if plates and screws are used the wound should be left open. It is admitted that in some cases in which there is little or no swelling or trauma to the soft parts closure of the wound can be done after internal metallic fixation, but such treatment should be undertaken only by surgeons of wide experience and sound judgment. If the slightest evidence of infection becomes manifest, the wound should be widely opened, plates and screws exposed but not removed and the Carrel method instituted, it having been made sure that the tubes have been inserted in every pocket or recess. It is extremely hazardous to use metal fixation in compound fractures unless the wound has been carefully debrided and the Carrel treatment instituted immediately. The theoretic objections to the use of metallic substances in compound fractures are based on faulty and incorrect conclusions due to inexperience and opinions handed down before the

acceptance of debridement as a fundamental principle and the Carrel technic as a definite prophylaxis against infection

For the past thirty years, vanadium steel has been used in plates and screws because of its great physical and metallurgic properties. When exposed to sodium hypochlorite, these steel plates corrode, and as a result of the oxidation due to the deposit of ferric oxide staining takes place. As a result, 60 per cent of the plates and screws used in compound fractures must be removed. I usually remove plates and screws if the wound is unhealed in five to seven weeks after insertion of the foreign bodies.

The objections to vanadium steel have been overcome recently by the production of a new stainless steel (chrome, 18 per cent, nickel, 8 per cent, molybdenum, 2.38 per cent, Rockwell hardness, C scale, 35 to 37), which has all of the physical properties of vanadium steel and will not corrode in the presence of sodium chloride or sodium hypochlorite solutions. It is much superior in physical properties to vitallium, which is objectionable because it is cast metal, is entirely too brittle and contains air bubbles. This new alloy steel is the solution to the question of the use of metals where screws, plates, nails and other metal fixative devices are used. Should they be removed, they can be used again. Metals such as monel and duralumin should not be used because of the tendency of the copper in the monel metal to corrode and because duralumin likewise has a tendency to corrode and effloresce in the presence of saline solution. Electrolysis does not occur when like metals are used.

CONCENTRATED SOLUTION OF SODIUM HYPOCHLORITE AND SODIUM CHLORIDE (HYCLORITE N N R)

Sodium hypochlorite (bleaching lime) has long been known as a powerful disinfectant and deodorant. Semmelweis' epochal discovery is well known to any one familiar with the story of antiseptics. Many hundreds of antiseptics, too numerous to mention, have been advocated for prevention of wound infection as well as for treatment of infected wounds but have been proved absolutely worthless when put to a clinical test. The action of an antiseptic in a test tube or Petri plate is entirely different from that of an antiseptic in actual body wounds.

In the early years of the World War (1914 and 1915), every antiseptic known at that time was tried both to prevent wound infection and to control it when once present, without success. Carrel and his co-worker Dakin again reverted to the use of sodium hypochlorite, but because of its instability when exposed to air it was necessary to have a lime of known chlorine activity in order to make a 0.5 per cent solution of sodium hypochlorite. The solutions were unstable and more or less

caustic, necessitating frequent titrations and the making of a fresh solution every few days. The solution, while strongly antiseptic, was absolutely nontoxic, and a solvent of necrotic tissue did not destroy living cells or tissues. Liquefaction by oxidation of necrotic tissue removes from the wound the culture mediums on which many bacteria thrive.

In 1918, an electrolytic process was evolved in the manufacture of a concentrate (sodium hypochlorite 4.05 per cent and sodium chloride 3.25 per cent) of low alkalinity, p_H 11. This solution is relatively stable, losing approximately 10 per cent active chlorine per year. Its use has greatly simplified the Carrel treatment in that it eliminates the daily titrations and the making of a solution every few days. The addition of $6\frac{1}{2}$ parts of water to 1 part of the concentrate makes a solution of proper strength as to both sodium hypochlorite and sodium chloride content and is vastly superior to solutions made from sodium hypochlorite or liquid chlorine. The commonly used term "chlorinated soda" does not sufficiently specify the nature, quality or content of sodium hypochlorite. This concentrate when diluted $6\frac{1}{2}$ to 1 is hypertonic, greatly increasing osmotic action and the flow of phagocytes and lymphocytes into the wound, and there is no danger of dehydration of the body, such as is produced by salt packs with the technic of Sir Almoth Wright. One frequently hears that the same results can be secured with physiologic solution of sodium chloride. Such statements are based on lack of knowledge of chemistry and of the physiologic action of sodium hypochlorite and on inexperience so far as the technic of Carrel is concerned. The incidence of infection in time of peace should be practically nil. The environment, the nature of the wounds and the presence of foreign material (multiple shell fragments, soil and clothing) do not permit as careful asepsis in war as in peace. However, the standardization of treatment from "firing line to base" in the British Army at the Salonika front from 1915 to 1918 (debridement, sodium hypochlorite irrigation, etc.) tremendously reduced the mortality and the number of amputations and wound infections. A visit to the clinic of DePage at LaPanne, Belgium, disclosed 80 compound fractures undergoing treatment without a single infected wound. Sepsis and infection of wounds were completely controlled in injuries treated within the first six to eight hours. Visits to every other hospital, except for three where the Carrel method was carried out, revealed infection in every compound fracture (May to November 1916).

A most scrupulous instrumental technic and most careful asepsis with attention to sound and generally accepted surgical principles must be adhered to if success is to be assured. The principles are simple and can be easily executed by surgeons and nurses who have received instructions who have an understanding and who are intent on carrying on the technic without alteration.

NONUNION FOLLOWING COMPOUND FRACTURES

Nonunion is a more frequent complication in compound fractures than in simple fractures, but it is important that it be differentiated from delayed union. Application of an autogenous bone graft, either inlay or onlay, is usually the treatment of choice. The graft should be firmly affixed to the host and immobilized by transfixion with two to four stainless steel (chrome-nickel-molybdenum) screws.

After operation, plaster splints completely immobilizing the fracture should be used until union occurs. The Morton Smart technic of graduated contraction of muscle should be instituted as soon as union takes place, as it not only restores muscle tone rapidly but increases the circulation to the extremity.

If postoperative infection occurs, the wound should be opened widely and Carrel tubes inserted into every recess and cavity, the hypochlorite solution being injected every two hours until the wound is free from gross infection. Infected wounds usually cicatrize, leaving one or more sinuses leading to the steel screws. This is due to corrosion or oxidation of the steel. After union has taken place, the screws can readily be removed. When the initial treatment of careful debridement and the Carrel technic with hypochlorite solution has been properly done postoperative infection seldom occurs, as one is operating in a field that has been noninfected.

If osteomyelitis or infection has complicated the healing of a compound fracture, resulting in nonunion, the bone-grafting operation should be delayed from six to twelve months. Despite delay in grafting, infection not infrequently follows in cases in which chronic osteomyelitis and infection have existed for a long time. The clinical appearance is normal, and one is apt to find evidence of walled-off infection in small foci which are activated by the operative procedure, resulting in the failure of the bone-grafting procedure. Repeated bone grafts, two and sometimes three, are necessary in these cases before strong bony union is secured. The prolonged convalescence could have been materially reduced had the initial treatment of debridement, immobilization and the Carrel method been instituted.

CONCLUSIONS AND RESULTS

Since January 1917, a period of twenty-three years, the treatment of compound fractures by debridement, with the Carrel technic, reduction of the fracture by internal or external fixation and immobilization has been standardized in this clinic. There were treated a total of 11,127 compound fractures (not inclusive of traumatic amputations and fractures of the skull, chest or pelvis), of which 630 were fractures of the long bones, with the following results:

One amputation of the leg due to loss of soft parts. One third of the shaft of the tibia had been destroyed at the time of the accident.

Three amputations of the leg due to thrombosis and secondary hemorrhage, with extensive destruction and crushing of the bone and soft parts. Despite gross trauma, an attempt was made to avoid amputation, to no avail. In all 3 of these cases the leg should have been amputated at the time of admission.

One amputation due to frank infection.

Eighteen amputations of phalanges due to destruction of blood supply and loss of soft parts.

No cases of sepsis.

Two deaths, one from an embolus a few days after admission and the other from shock following a reconstruction operation.

The results secured are ample evidence of the soundness of the principles employed. I am not in accord with the methods being advocated in Europe of nonpadded plaster, closed technic of treating compound fractures. I fully realize that such methods may be necessary as a war emergency. However, when time and environment permit accurate reduction of the fracture, debridement and the Carrel technic with immobilization either by plates or by splints is the best procedure and is certain to bring about the best functional results in the shortest period, with a minimum of deaths, sepsis and amputations.

COMPOUND FRACTURES

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AND

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The present treatment of so common an affliction as a compound fracture has to a certain extent reached a fixed stage. As with any fracture, factors (such as shock, hemorrhage, or cerebral injury) which threaten the life of the patient must be attended to before anything more than immobilization of the fracture by the simplest means is attempted. Ideal débridement with immobilization until union has occurred is recognized as utopian. The proper technic of débridement, however, and the proper treatment of the wound after débridement are still points of debate, and it is these points which are to be investigated in this study. Numberless essays have been presented dealing with the treatment of compound fractures, each citing the method particularly favored by the writer, with a list of his favorable results as supporting evidence of the superiority of the method discussed. These authors vary from those who would recommend sewing the débrided wound layer by layer, tightly, as a clean wound, and those who would recommend irrigation of the open wound with a chlorinated solution designed to dissolve dead tissue to those who would pack the débrided wound wide open with petrolatum gauze and allow the pack to be extruded from the base of the wound by the advancing walls of granulation tissue. Such diversity of opinion not only indicates the lack of an entirely satisfactory method but emphasizes that whatever the method is, it is good in the hands of those who are familiar with its technic.

The healing of broken bones is in itself a problem so complex and so strikingly influenced by accessory factors that in general it has no immediate place in this paper. However, in so far as factors which present themselves in compound fractures influence wound healing and bone healing, a discussion of these contributory factors is important. The outstanding factor is infection. This investigation is an attempt to

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evaluate certain ideas in regard to treatment of compound wounds, especially those sustained in dirty surroundings. That other interesting associated facts present themselves in analysis is assumed.

PROBLEM AND SOURCE OF MATERIAL

The specific aim of this analysis is to investigate the incidence of wound infection in compound fractures in two groups of cases. One group was treated by thorough sharp debridement, followed if necessary by cleansing of the interior of the wound with copious floodings of bland solutions, such as saline solution or soft soap U S P (green soap) followed by saline solution. For the second group almost the same routine was utilized, the difference being that iodine and alcohol were introduced into the depths of the wound after it had been debrided, before closure and sometimes before debridement.

The material studied consisted of the rank and file of compound fractures observed in the "male fracture ward" of the Cook County Hospital. A few cases were not included because they were classified under another heading, the cases of a few women and children are included because the patients were cared for by the resident surgeons from the "male fracture ward." The number of cases was 131. The details of treatment were almost identical. The fracture was temporarily splinted, and the patient was examined for associated injuries. Such factors as hemorrhage, cerebral injury and shock, which might jeopardize the life of the patient, were treated, it was not until treatment of the fracture was deemed imperative or safe that the injured member was given definitive care. At that time the palpable distal pulses were investigated, the viability of the distal part assayed, the fracture studied and the most feasible means of immobilizing the fracture considered. Anesthesia was induced (most often ether anesthesia or local anesthesia in this series) and the extremity unsplinted. The compound injury was then covered with sterile dressings, and the entire surrounding skin was cleansed, shaved and painted with iodine and alcohol up to the cutaneous margins. After the field was draped as for a major surgical procedure, the most gross foreign material was picked out of the interior of the wound. Then with a sharp scalpel a rim of skin was excised from the edge of the wound, and the underlying soft tissues were removed en bloc as sharply as possible, the instruments used being changed several times in order to minimize contamination of the freshly produced surfaces. Nothing except indispensable tissue such as tendons, blood vessels and nerves, was spared. The bone, such as it was, was scraped or washed. Bony fragments, if freed from soft tissue, were lifted out of the wound. Gross hemorrhage was arrested by ligation of bleeding points. The wound was then closed with the aid of accomplishing layer by layer approximation without suturing.

closure that wound secretions would accumulate or that postoperative swelling would produce necrosis. The skin was usually closed by silk-worm gut, with a surgeon's knot, which could be manipulated at each dressing to accommodate the state of the tissue swelling.

Although it was not possible to expose the closed wounds to the air, every attempt was made to maintain dryness of the wounds and in particular to change the dressings when the serosanguineous discharge was sufficient to keep the dressings moist. This had a twofold purpose (1) to prevent retrograde infection from cutaneous saprophytes into wet dressings and thence into the wound and (2) to utilize the capillarity of the dressings to remove undesired accumulations of fluid beneath the edges of the skin. As soon as a solid crust had covered the edges of the skin, the dressings were removed and the wound allowed to remain exposed to the air.

In the cases in which iodine and alcohol were introduced into the wound, the aforementioned technic was used except that the débrided wound was either painted or flushed with these drugs. Such devices as relaxing cutaneous incisions and incisions for counterdrainage were used as needed. In no case were packs inserted into the wound. In 1 case Dakin's treatment (with diluted solution of sodium hypochlorite U S P) was started but was abandoned soon. In a few cases there was such loss of tissue that primary closure was impossible.

Before progressing to the discussion of statistics, it should be emphasized that no two cases are similar and that even in a relatively large group, such as this one, there are enough varied factors almost to nullify the value of comparison of the therapeutic methods. There are rarely two wounds in the same region of a bone with equal amounts of comminution, equal amounts of contamination and an equal amount of damage to the blood supply. The final outcome is also influenced by such factors as the age and general health of the patient and his ability to withstand the shock of the accident. The last-mentioned factor is rarely adequate in the average patient who presents himself for care at the Cook County Hospital.

STATISTICS CONCERNING FRACTURES

The general distribution of the fractures in this series of 131 patients was as follows:

Ninety-three, or 70.9 per cent, were fractures of both bones of the leg.

Eighteen, or 14.2 per cent, were fractures of the humerus and forearm.

Ten, or 7.6 per cent, were fractures of the hand.

Seven, or 5.3 per cent, were fractures of the femur.

Two, or 1.0 per cent, were fractures of the patella.

One, or 0.7 per cent, was a fracture of the olecranon.

From a different point of view, especially in regard to further analysis, the fractures in the 131 cases were studied with regard to the following facts

There were 31 deaths

Six patients came in six to eight days after injury, having been treated elsewhere, 3 of these were infected

Six patients signed a release and left the hospital

Eighty-eight patients lived and were finally dismissed from the hospital Half of this number were treated with iodine in the wound and half without

Deaths—Perhaps the most startling figure is the high number of deaths In the following list they are classified as to cause These being traumatic are coroner's cases, and the patients are usually signed out under the blanket diagnosis of "shock and hemorrhage," with no autopsy

Death terminated 31 of 131 cases (24.2 per cent)

Ten deaths were from shock or cerebral injury (within twenty-four hours)

Seven were from delayed shock, bronchopneumonia, etc

Three were from delirium tremens

Three were "anesthetic deaths"

Two were from internal hemorrhage

Two were from gas gangrene

One each was due to "pulmonary embolism lobar pneumonia," post-operative intestinal obstruction and accident

Probably in the first group of patients death was inevitable, and only because of the efficiency of the police force in bringing seriously injured patients to the hospital on discovery did the patients live long enough to enter the ward The second group of patients were those who never satisfactorily rallied from their original injury and within a week, or perhaps less, slipped, became semicomatose, had bronchopneumonia and died In this group there was 1 patient who died of wound infection He was admitted to the hospital only four hours after his accident but with unmistakable signs of sepsis, the edges of the wound being reddened, he already had fever and presented an exhausted appearance He lingered six weeks before death There were 2 cases of gas gangrene, both of the patients were severely injured One of them was treated with iodine and the other without Both died after amputation of the contaminated extremity The group of cases of internal hemorrhage and "anesthetic death" is embarrassing The 2 patients with internal hemorrhage seemed clinically to have a crushing wound of the chest with massive intrapleural hemorrhage One of the "anesthetic deaths" occurred in a man aged 50 who had a fractured humerus His death was sudden occurring during the first whiffs of the ether

The symptoms were interpreted as indicating an attack of coronary occlusion. The other 2 patients were men with severe injuries to the leg who presumably had more cerebral injury than was apparent clinically. There were 1 patient who died suddenly of pulmonary embolism on the second day of hospitalization, 1 with lobar pneumonia, and 3 who suffered from delirium tremens. Two of the last-mentioned patients had suffered from severe injury, and the psychotic episode developed within twelve hours after injury. In these cases the diagnosis of fat embolism might have arisen. In 1 the fundi did not show evidence of fat emboli. The patient in the third case was a man with a compound fracture-dislocation of the ankle, whose symptoms developed twenty-four hours after injury and who died within six hours after their appearance.

It is interesting to note the following distribution of the 31 deaths according to fracture:

Twenty-six, or 83.6 per cent, of the patients who died had fractures of both bones of the leg.

Three, or 9 per cent, had fractures of the femur.

Two, or 7 per cent, had fractures of the arm.

The mortality rate for the various fractures is indicated in the following data:

Seven were fractures of the femur, with 3 deaths (42.8 per cent).

Ninety-three were fractures of the leg, with 26 deaths (28.0 per cent).

Eighteen were fractures of the arm, with 2 deaths (7.0 per cent).

Infections—On this subject, which is the main point of interest of this paper, we present the following statistics, based on the cases of the 88 patients who survived and finally left the hospital. In patients treated without iodine and alcohol, infection occurred in 6, or 13.1 per cent; with iodine in the wound, it occurred in 8, or 18.1 per cent—a slight difference, since the numerical case difference is only 2. However, of the 31 patients who died, there were 11 whose wounds showed evidence of infection. In 2 of these there was definite gas gangrene. One patient (mentioned previously) died from his infection. The other 8 showed varying amounts of infection, in most cases interpreted as resulting at least in part from the patient's general debility, since all infections (excluding gas gangrene) occurred in that group. In addition to the 11 patients who died of infection, there were 14 who survived.

Of the total of 25 patients with infection, 21, or 84 per cent, had fractures of both bones of the leg, and of 11 patients who died, all had fractures of both bones of the leg.

Comparison of the average number of days in the hospital for the patients with clean and for those with infected fractures shows a much longer stay for the infected patients. Including infected patients, the average number of days in the hospital was forty and three-tenths in the group which was not treated with iodine and alcohol in the wound and fifty-six and five-tenths for the group treated by this method. For the infected patients alone, however, the number of days in the hospital was respectively eighty-six and eight-tenths and eighty-one and five-tenths. Without much difference in the two groups, the number

Detailed Analysis of Cases in Which Fractures Were Treated in the Hospital

Without Iodine	Factor Considered	With Iodine
44	Number of cases (total)	44
40.3	Average number of days in hospital (total)	56.5
6	Cases of infection (total)	8
13.1	Percentage of infected wounds	18.1
86.9	Percentage of clean wounds	81.9
86.6	Average number of days in hospital	81.5
2	Number of fractured femurs	2
0	Number of infections	1
28	Fractures of both bones of the lower part of the leg	30
39.9	Average number of days in the hospital	67.5
5	Number infected	6
18.0	Percentage infected	16.6
100.6	Number of days in hospital (infected)	101
36.6	Number of days in hospital (clean)	40.5
17	Cases in which a Steinmann nail was used	26
60.0	Percentage nailed	80.0
13	Number of cases of fracture treated with a nail clean	20
82.0	Percentage nailed clean	76.0
39.5	Number of days in hospital nail, clean	66
5	Number of cases of fracture treated with a nail infected	6
18.0	Percentage nailed infected	16.6
100.6	Number of days in hospital, nail infected	102
10	Number of case immobilized with plaster	6
35.0	Percentage treated with plaster	20.0
36.5	Number of days in hospital with plaster	40.5
0	Number of infections with plaster immobilization	0

of days in the hospital was practically doubled with the development of infection. The duration of hospitalization is admittedly long. We were forced to hospitalize some who might have been treated as outpatients because we could not depend on them to return to the follow-up clinic.

Patients Treated Elsewhere—For the 6 patients who were not given primary treatment by us the rate of infection was 50 per cent. These patients came in from six to nine days late, often with packs deep in the wound, no debridement and inadequate immobilization. One had a well-developed gangrene and recovered after multiple incisions and prolonged primary dressings.

Classification of Fractures—It is noted from the data presented that 28 of the 44 fractures were fractures of both bones of the lower part of the

number alone justifies their being considered separately, but their importance is even greater because of the difficulties of obtaining satisfactory limbs in these cases. Such injuries are often contracted by direct violence from an automobile accident, especially from bumper injuries. The tibial crest is subcutaneous and easily injured, the fracture is very easily compounded, and, since the accidents occur in the street, usually the contaminating materials are the worst. Add to that the recognized difficulty in covering the fractured tibial crest with viable tissue (particularly after loss of tissue) which will not slough on tension and the known sluggishness of tibial fractures in developing adequate callus, and their importance pyramids.

In discussing these cases it should be noted that there was no rule which decided the method of immobilizing the fracture. The choice as to whether a Steinmann nail was used depended on the judgment of the resident surgeon. It may be noted that 60 per cent of the fractures treated without iodine were treated by skeletal traction, while 80 per cent of those treated with iodine were so treated. This, no doubt, added to the number of days in the hospital for the latter group. As conditions varied it occasionally became necessary to change from primary immobilization in plaster to skeletal traction. In none of the cases in which immobilization in plaster was used throughout did infection occur. This may be explained either because the size of the compound injury was slight or because frequently with the development of infection the treatment was shifted to skeletal traction.

Steinmann Nail—In this group there were 3 infections about Steinmann nails. No nails pulled through the os calcis.

Interval Before Treatment—Another important factor is the interval between injury and debridement. After attempting to classify these cases, we finally arrived at the conclusion that there is a fair chance of obtaining a clean wound if the patient is treated within eight hours after injury. We observed several wounds which were clean and which were debrided for the first time twenty-four hours after injury, 1 death occurred in a case in which the patient was seen within four hours after injury. In this case the wound seemed infected on entry. In the group which came in late (twenty-four hours to nine days) the percentage of wound infection was 50 and would undoubtedly have been higher had not some of the patients been given good care elsewhere.

Gas Gangrene—There were 3 cases of gas gangrene, 2 of the patients died. In the cases of these 2 there was only a short interval between the injury and the development of severe signs of sepsis. The third patient entered the hospital late, with mild symptoms of sepsis, gas gangrene was detected, but he recovered.

Size of Cutaneous Defect—The size of the exposed wound is a terrifying factor at times. More important than the size of the cutane-

ous opening is the extent of internal avulsion of the tissues. If the periosteum is avulsed from the bone, if the bone is fragmented, if the vessels are torn and occluded and the entire wound crushed, these factors outweigh the size of the cutaneous injury. There were 2 patients listed here as infected who were interesting from this point of view. Both presented themselves with severe comminution and avulsion of the periosteum of the tibia, with great loss of tissue. In 1, some 14 inches (35.5 cm) of tibia was denuded of periosteum and surrounding muscle. The legs were cleansed, debrided and immobilized with skeletal traction. For fourteen days the patients showed no signs of infection, no fever and no discharge. At the end of that time, however, a slight increase in the amount of serous discharge from the open wounds was noted, and finally, after three days, the discharge became frankly purulent. Even then the patients had no fever, and the infection did not spread beyond the confines of the exposed bone. Later, in the exposed marrow cavity, granulation tissue could be seen filling the cavity, and it also sprang from the viable bone. Still later, large pieces of bone became loose, and the avulsed periosteum laid down new bone. Our explanation was that the wound had been clean after debridement, had we been able to close the skin or had the injury not been compounded, the bony fragments would have been absorbed and replaced with no ill effects. However, in these open wounds the dead bone, acting as a foreign body, eventually had become secondarily infected.

Follow-Up—We have a saying that “only the bad results come back,” but it is hard to believe that the percentage of good results is as high as such an interpretation would indicate. A more satisfactory follow-up might throw light on such important questions as final results and the influence of infection on callus formation. Unfortunately, the percentage of follow-up in these cases was too low to allow formation of definite conclusions as to the final results.

COMMENT

A wound which can be debrided properly is a wound which has been seen as a contaminated and not yet infected wound. Careful excision of all contused tissue and removal of foreign material are done, the aim being to convert the area into a clean surgical wound. However, once contamination has occurred, it is doubtful that any debridement, however careful, can be ideal. One must picture a few lurking organisms in the depths of the wound. Nevertheless, the body tissues are in direct contact with the center of the wound, the tissue juices can pour into this area, and in the absence of necrotic tissue the local defensive mechanisms may attack these organisms and then allow normal healing of the wound to occur.

We base our avoidance of powerful antiseptics in the depths of the wound on a fact of comparative anatomy. In man the skin is able to withstand external trauma and has taken over the ordinary protective functions of the rest of the body. As would be expected, the underlying tissues, relieved of the necessity of protecting themselves from external violence, have diminished powers of self preservation and hence cannot tolerate contact with powerful antiseptics which do not harm the skin.

Picture, then, a wound after careful debridement to which one has added application of iodine and alcohol. Alcohol is an excellent tissue coagulant, and this mixture of iodine and alcohol lines the wound with a layer of coagulated tissue proteins. Adding iodine and alcohol does not sterilize the interior of the wound, it injures the walls of the wound, and the bodily defenses now have to handle the layer of dead cells lining the cavity as well as to attack the organisms in the wound. The organisms, on the other hand, find themselves protected from the bodily defenses by the coagulated tissue and have time to gain a foothold. Such an apparently slight factor may decide whether the wound will remain clean.

SUMMARY

A study of 131 consecutive compound fractures has been made. There were 31 deaths. A detailed analysis of 88 cases is presented, in 58 there were fractures of both bones of the leg, and in only 4 were there fractures of the femur. Immobilization was secured by Buck's extension, plaster or skeletal traction with Steinmann nails. It is felt that if the patient is seen within eight hours after injury a fair chance for effective debridement is offered. Adequate debridement should remove all foreign material and dead tissue, sparing only indispensable tissues. In half the cases the debrided wound was flooded with iodine and alcohol before closing, in half it was not. In 18.1 per cent of patients treated with iodine and alcohol, infection developed, in 13.1 per cent of those treated without iodine and alcohol, infection developed. In the group treated with iodine and alcohol, hospitalization extended over fifty-six and one-half days for uninfected patients and eighty-one and one-half days for the infected group. In the group treated without iodine and alcohol, hospitalization lasted forty and one-half days for the uninfected and eighty-six and one-half days for the infected patients. The comparison of days of hospitalization in the cases in which infection occurred is probably not of much significance, because of the importance of the resultant osteomyelitis in the duration of the therapy. As has been stated, our analysis shows a definitely greater incidence of infection in the wounds treated with iodine. This is explained on the assumption that the use of iodine resulted in the death of a sufficient number of cells to encourage infection.

COMPOUND FRACTURE THERAPY AT THE BOSTON CITY HOSPITAL

OTTO J HERMANN, M D

BOSTON

In 1937 I published a paper on the treatment of compound fractures¹ That paper was based on the work done during the period from 1924 to 1934, whereas this paper covers the work done exclusively in the bone and joint service of the Boston City Hospital during the period from 1934 to 1939 Naturally, a considerable part of the earlier paper is incorporated in this one

During the five year period from July 1, 1934 to July 1, 1939, there were 12,230 patients with fracture admitted to the Boston City Hospital as requiring "house" care This number does not include the many hundreds of patients with fractures of the "immediate ambulatory" type treated on the accident floor or in the outpatient department Of the 12,230 hospitalized patients, the bone and joint service treated 4,491, of whom 398 had the "open," or compound, type of fracture It is the management of this type of fracture which I shall discuss

Before I go into the actual discussion of compound fracture therapy, I shall present some data which I gathered from the records of these cases

GENERAL DATA

Age Distribution—The age incidence was as follows

1 to 10 years	10 per cent
10 to 20 years	17.1 per cent
20 to 30 years	10 per cent
30 to 40 years	12.7 per cent
40 to 50 years	19.2 per cent
50 to 60 years	17.7 per cent
60 to 70 years	9.3 per cent
70 to 80 years	4 per cent

Skeletal Distribution—The fractures occurred in the following bones (listed in order of percentage)

Both bones of the lower part of the leg	28 per cent
Both bones of the forearm	13.5 per cent
Fingers (phalangeal)	10.3 per cent

¹ Hermann, O J Treatment of Compound Fractures, New England J Med 217:909, 1937

Ankle	9 5 per cent
Femur	6 4 per cent
Tibia	5 3 per cent
Toes	4 8 per cent
Thumb	4 per cent
Humerus	3 9 per cent
Metacarpal bones	3 per cent
Wrist	2 5 per cent
Ulna	1 5 per cent
Olecranon	1 5 per cent
Os calcis	1 1 per cent
Metatarsal bones	0 8 per cent
Nose	0 8 per cent
Skull	0 8 per cent
Elbow	0 5 per cent
Radius	0 5 per cent
Astragalus	0 5 per cent
Patella	0 2 per cent
Ilium	0 2 per cent
Tarsal scaphoid bones	0 2 per cent
Spine	0 2 per cent

Causation —It was interesting to note that 20 per cent of the patients had multiple injuries, of which about two thirds were caused by the automobile

The causes of fracture were as follows

Automobile accidents	37 7 per cent
Falls	36 2 per cent
Crush injuries	23 2 per cent
Miscellaneous injuries (caused by bicycles, horses, guns, wagons and trains)	3 per cent

Hospitalization —The average period of hospitalization in 100 consecutive cases was twenty-seven and twenty-four hundredths days per patient. These stays ranged from one to one hundred and thirty-two days

Mortality —There were 23 deaths recorded for the 398 cases. Fourteen patients died shortly after entry into the hospital (minutes to twelve hours), and all had multiple injuries and were simply given local surgical first aid plus the usual shock therapy. Two of the remaining deaths were caused by delirium tremens and 3 by pneumonia, 1 patient died after a cerebral hemorrhage thirty-six hours after entry, and 1 died of embolism four days after entry. Two died after primary amputation,

both with multiple injuries, and 1 died after a secondary amputation for gas bacillus infection forty-eight hours after injury (The last-mentioned patient had a massive, dirty compound fracture of the lower part of the left leg, involving the knee, the "first aid" treatment consisted in application of a dirty rope tourniquet and a manure-soiled plank for a splint, and the patient was brought to the hospital on the floor of a taxicab!)

Sepsis—Sepsis occurred in 28 cases. This ranged from mild local wound infection to virulent sepsis and osteomyelitis. Five of the patients reported to the hospital from twelve to thirty hours after injury and were already infected or practically so. The other 23 patients showed the following types of sepsis. Sixteen had local wound infections which cleared up in periods ranging from one to four weeks, three had local osteomyelitis (in 1 case a thumb with a compound fracture caused by the bite of a vicious dog had to be amputated), and 3 had gas bacillus infection (2 of these came to amputation, and the infection of the other cleared up under local and general therapy). It is also to be noted that of the 23 wounds 4 were initially left open and treated by the Oir method and 2 were left open and dakinized (treated with diluted solution of sodium hypochlorite U S P), the remainder were given primary suturing.

Properly, the treatment of the compound fractures observed over this five year period should have begun at the scene of the accident. Unfortunately, the first aid treatment in these cases was for the most part crude and did more harm than good. However, this situation is, I sincerely hope, now corrected, owing to the dogged perseverance and work of Dr. William Reggio in connection with the local police department.

TREATMENT

Initial Measures—Treatment of compound fractures in this hospital, as has been mentioned, begins on the accident floor. There an examination is made of the patient as a whole by one physician while the compound injury and the patient are given initial treatment. Because of the terrific smash injuries by automobiles today, the general examination must be carefully carried out. The examiner has to bear in mind all sorts of complications. Besides shock and hemorrhage, he must look for injuries to the skull, the spine, the chest, the kidneys and the abdominal viscera and many other things. The large number of cases of multiple trauma makes this paramount today.

The initial treatment consists in immediate institution of shock and hemorrhage therapy (heaters, blankets, morphine), exposure of the compound fracture and its immediate covering with a sterile dressing.

Then come removal of all clothing and temporary traction and fixation of the fracture by a Murray-Jones arm splint, a Keller-Blake leg splint or a "pillow and sides" splint, as the condition requires. After this preliminary examination and treatment, if the patient's condition is satisfactory a roentgen examination is made, and the patient is then taken to the operating room.

If, however, the patient is in severe shock on arrival, he is at once transported to a shock room, where he is put into a shock bed equipped with blankets and electric pads. He is given morphine, his clothing is removed, the wound is dressed and the fracture is temporarily splinted (As much as possible of this is done under blankets). Treatment of the shock is then continued along the lines suggested by one of the staff members, Dr. Kenneth Coonse. At this hospital my associates and I still have to depend on the not too accurate method of gaging traumatic or hemorrhagic shock by the systolic and diastolic blood pressure. Any pressure below 90 is potentially dangerous, and any pressure which persists below 80 is insufficient for adequate circulation in the peripheral tissues. As Coonse has stated, it is important in cases of surgical shock to institute prompt treatment sufficient to restore an adequate level of blood pressure, together with adequate red corpuscles and serum proteins. This, of course, is best accomplished in the majority of cases by transfusion of whole blood. In cases of severe shock, restoration of the blood volume is the first and most important procedure. As no "blood banking" system has been established at our hospital, a definite interval elapses between the patient's arrival at the hospital and the actual transfusion. This time is valuable, and so while waiting for the typing and the donor we make use of a special sodium bicarbonate solution in combination with hypertonic dextrose or saline solution, as directed by Coonse. This sodium bicarbonate solution is of about 7 per cent strength and comes in 50 cc ampules. It is given if necessary at half-hour intervals until the transfusion is actually being given. The blood is given generally in citrated form (though some still give whole blood by the Kimpton tube method) and amounts to about 500 cc. As a rule the patient responds rapidly to this intravenous sodium bicarbonate treatment and in the majority of cases can be taken to the operating room via the x-ray room within an hour of arrival at the hospital. This fact, I believe, has aided greatly in lowering the incidence of sepsis.

In all cases, after testing and desensitization a prophylactic dose of 100 cc of gas gangrene antitoxin and 1 500 units of antitetanus serum are given intramuscularly. Patients having large macerated wounds or extremely dirty ones are given the same amount of gas gangrene antitoxin with 5 000 units of antitetanus serum, and this dose is repeated twice during the first ten days.

Anesthesia—The type of anesthesia is selected by the surgeon and the anesthetist after a check-up of the patient's local and general condition. The types of anesthetic used are spinal anesthetic agents, nitrogen monoxide and ether, nitrogen monoxide and oxygen, avertin in amylene hydrate with ether, intravenous pentothal sodium with or without a local anesthetic and, occasionally, local anesthetics. Cyclopropane is also given when indicated.

Preparation of the Wounded Area—As soon as full anesthesia has been attained, an assistant removes the temporary splint, maintaining traction, while a second carefully shaves the limb about the wounded area. If the skin is covered with oil or grease, a careful preliminary cleansing with benzine or ether is done by the second assistant. This cleaning is all done with the wound carefully covered with sterile gauze, which has replaced the initial dressing after material for a "wound culture" has been taken.

With this sterile dressing carefully held on the wound, an assistant who is scrubbed and is wearing sterile gloves begins a thorough centrifugal cleansing of the skin surrounding the wound with soap and water. The cleansing is done by sterile gauze pads, and at least fifteen minutes is consumed in this. The skin is then carefully wiped with gauze soaked in saline solution followed by ether.

This assistant now changes his gloves, removes the sterile pad from the wound and replaces it with one that just fits the wound itself and not the edges. The edges are then given a cleansing with soap and water followed by ether. Again the assistant changes his gloves, soap and water, removes the pad from the wound and proceeds to clean the wound itself with sterile gauze and water and soap, following this with an ether wash.

Debridement—The surgeon steps in and drapes the wound in the usual manner after wiping the skin and then the wound with ether or alcohol or, sometimes, painting it with a 2 per cent iodine solution. He then proceeds to excise the traumatized lacerated edges of the wound, generally to a width of not more than $\frac{1}{8}$ inch (0.32 cm). This is done cleanly with a forceps and a knife. Extreme care must be taken not to excise too much of the edge of the skin. The operator then changes instruments and commences the debridement proper. During this, gentle irrigation with warm salt solution is going on. No forceful stream is used.

In regard to debridement proper, the technic described by Wilson and Cochrane² is, with some exceptions, essentially followed.

² Wilson, P. D., and Cochrane, W. A. *Fractures and Dislocations*. Philadelphia, J. B. Lippincott Company, 1925, pp. 49-57.

General Details of Technic For the operation itself, the most careful technic is required. The surgeon should employ instruments altogether in handling of tissues and avoid putting the gloved finger into the wound. A frequent change of soiled instruments for fresh sterilized ones is necessary, and if the gloves become contaminated from the wound, they should be immediately changed, or carefully washed in strong antiseptic solution. Great pains must be taken to avoid traumatization of healthy tissues by seizing them roughly with forceps.

Retractors should be used gently. Sponge by pressure rather than by wiping, as the latter spreads infection into sterile parts. Careful hemostasis must be obtained as blood clots favor the growth of bacteria. Avoid ligation *en masse*, as the tissue tied off is deprived of blood supply and furnishes excellent media for organisms. Deep sutures and ligatures should be made with fine catgut and the knots cut short. Suture and ligature material constitute foreign bodies and favor the development of infection.

The operation is best performed by the method of progressive excision of the walls of the wound. When possible this may be done by block removal to a considerable extent, but it is never possible to deal with the entire wound in this manner, and the danger is always in the excision of too much tissue. The surgeon should be especially warned against this fault, as it is one that has frequently brought the operation into disrepute.

Excision of Damaged and Infected Tissues The external wound opening should be excised with a surrounding strip of skin 7 mm to 1.25 cm wide. Complete access to the wound should then be obtained by an appropriate incision. The subcutaneous tissue, being less important, may be removed more widely. The walls of the wound where they are distinct may be excised *en bloc*. When this is not possible, the surfaces should be carefully inspected and damaged and soiled tissue removed whenever found. When the blood supply is good, as indicated by free bleeding, it is sufficient to remove a layer 6 mm thick. If, however, the normal oozing is absent, the tissue should be excised. Blood clots should be removed and bloody infiltrations traced back along the fascial planes. Lacerated tendon sheaths should be opened and the tendons, depending on their condition, either removed or thoroughly cleansed.

Treatment of Muscle Tissue Muscle tissue should be treated with great care. It should never be sectioned transversely beyond the part which needs to be removed, as it does not regenerate and there is also likely to be injury of the minute nerve fibers running within the muscle itself. However, it is the favorite site for the development of gas infection, and all damaged and soiled tissue must be thoroughly removed. Healthy muscle may be recognized by its normal color, the oozing of minute drops on section, and its contractile response on stimulation with forceps.

In a modified way this technic has been followed by my associates and me. It must be emphasized that excision *en bloc* requires extremely good surgical judgment. It would probably be safer to recommend generally a careful, systematic removal of devitalized tissue wherever found. It is only the occasional fresh compound fracture that we enlarge by incision into neighboring tissue. It is our belief that the procedure is unnecessary in most cases and only adds more trauma, opening fresh tissue and thereby increasing the possible incidence of sepsis. It should be limited to the few instances in which internal fixation is needed, where there is considerable underlying traumatized and devitalized tissue.

or in which a simple plastic operation is to be done. Again, though we remove blood clots, we believe in not disturbing the fascial planes to any considerable extent in tracing bloody infiltrations. Also, we are ultraconservative in dealing with tendon sheaths and tendons.

Irrigation—After the debridement the wound is thoroughly but gently irrigated with warm salt solution followed by an ether wash, care being taken to avoid the bone and its coverings in performing the latter.

Treatment of the Fracture Proper—The surgeon now again changes his gown and gloves and redrapes the operating field. With an entire fresh set of instruments he treats the fracture proper. The fractured ends are gently curetted to remove all possible contamination, the instrument is discarded, and the wound is again gently irrigated. If the fracture is comminuted, extreme care is exercised in compact handling of the fragments. At this stage we bear in mind what Rutherford³ said in regard to this: "The leaving of bone fragments in a comminuted fracture is the surest way of securing natural and rapid repair, while the removal of these fragments is the surest way of securing ununited fracture."

We agree with him that it is extremely rare for a piece of bone in the ordinary compound comminuted fracture to be severed from all vascular supply. A piece of bone may be separated from the main shaft but not from the organically connected soft parts. Therefore, loose and comminuted fragments of bone should not be removed unless they are practically extruded from the wound and completely separated from all blood supply.

Choice of Procedure—From this point forward the treatment will proceed according to the surgeon's experience and judgment.⁴ I realize that some surgeons will proceed exclusively along conservative lines, that is, they will never plate, band, suture or nail this type of fracture. My associates and I unhesitatingly do so if we think the fracture requires it and if in our judgment the patient's condition warrants it.

Roentgen examination plays its part at this stage and often determines the decision between internal fixation and conservative treatment. Because of improved methods of enclosed fracture treatment it is found that only a small percentage of these fractures require internal fixation. But, as I have said, when a compound fracture needs internal fixation and the patient's general condition is good, we use it. Because of the relatively high incidence of delayed union and nonunion in these frac-

³ Rutherford, A. G. Management of Fractures of the Femoral Shaft, West Virginia M. J. 22, 6, 1926.

⁴ Forrester, C. R. G. Imperative Traumatic Surgery, New York, Paul B. Hoeber, Inc., 1929, chap. 18.

tures, accurate reduction and apposition are paramount. Internal fixation is sorely needed in some cases. In the selected instances in which my associates and I have felt the need of internal fixation and use it, we have found the wound remaining free from sepsis and giving relatively early good end results. Such results have shown us that the addition of the trauma of internal fixation to that of the original injury does not necessarily mean later sepsis. The use of such foreign materials as plates, screws and wires is not contraindicated because of their instigating later sepsis. Also, internal fixation has the advantage of absolute holding of the snug approximation, resulting in earlier union, it gives relief from pain, it prevents spread of infection, and it permits ease of handling of the patient, an all-important factor from the nursing and the convalescent standpoint. These arguments again uphold the contention that a great deal of judgment and experience is necessary before the surgeon can determine accurately the best method of treatment in each case.

The next stage of compound fracture therapy is controversial. Shall the wound be left open? Shall it be treated by the Orr method, by dakinization (irrigation with diluted solution of sodium hypochlorite U S P), by primary suture and temporary direct or dependent drainage or by simple primary suture?⁵ I have neither space nor time to go into the arguments for and against these methods. Each has its many ardent advocates. I believe that they are all good methods. I feel that the surgeon should use that method which in his hands, in his experience and in his surroundings has been kindest to him and his patients. However, he should not be absolutely dogmatic in regard to its use. Cases will be observed in which there can be no doubt of the superiority of one of these methods, and then it should be used.⁶ My associates and I happen to prefer as first choice the primary closure procedure without drainage. We have used it in roughly 85 per cent of our cases and the Orr method and dakinization in the remainder.

In compound fractures treated by the closed method the wound is closed in such a manner as to allow good tissue drainage, that is, no snug and sealed tight closure is attempted. These fractures are not drained by tube or by rubber dam. We depend entirely on our wide spaced type of suturing for tissue drainage. With this closed method we make certain that the exposed area of bone is covered. If we find that the edges of the wound can be brought together only by great tension or not at all we do not hesitate to promote closure by making

⁵ Graves, G. Y. Primary Suture of Compound Fractures. Review of Seventy Cases, *Am J Surg* **13** 539, 1931.

⁶ Scudder, C. L. The Treatment of Fractures, Philadelphia, W. B. Saunders Company, 1926. Cotton, F. J. Treatment of Compound Injuries, *Surg, Gynec & Obst* **52** 371, 1931.

lateral incisions on each side of the wound to allow the edges to be drawn together without tension. In cases in which this procedure is not sufficient a simple plastic operation is done. Above all, the wound should not be closed under tension, and there should be no exposed bone.

The open method is generally chosen by us when a good-sized area is involved, when there is considerable avulsion of tissue, when a considerable amount of dirt has been drawn into the wound, or when the patient has been in great shock and eight or more hours has elapsed since the accident. In such cases the fracture is treated finally by the Carrell-Dakin method or by the Orr petrolatum pack method. Later, when a smear shows a sterile field, a secondary repair of the fracture and the tissue is done.

Fixation—The final step in the initial treatment for compound fracture, after the appropriate dressing has been applied, is the application of fixation. Patients in whom internal fixation has been established need, as a rule, only some simple type of external fixation, such as a plaster of paris cast with an appropriate and well placed "window." Some may be held in a well fitting arm or leg Thomas splint or even the old-fashioned Buck apparatus. A large percentage of those who have been treated conservatively (i. e., without internal fixation) and in whom the fracture has been more or less easily reduced do well with the molded plaster of paris cast with "windows" over the wounded area. Fractures with a marked degree of overriding or comminution with displacement are put up in traction in a Thomas arm or leg splint, a Thomas leg splint with a Pearson flexion attachment, a Jones humeral extension splint or the simple "crotch" humeral extension splint. Patients treated with the Thomas splint are generally put in suspension traction on the Balkan frame or on a goose-neck abduction frame. The types of traction used are skin, Sinclair skate and skeletal (by Kirschner wire). I wish to warn against dogmatism as to the method used.

Unusual Fractures—There is one type of compound fracture which differs from the usual (frank) kind. It is the pinhole, or puncture, type. Surgeons are not unanimously agreed on the treatment of this type of fracture. It is said that about 75 per cent of such wounds heal immediately, but, even granting this to be true the surgeon who is confronted with an open fracture of this type can never be absolutely sure that it is not infected. The best basis for the treatment of such fractures is the assumption that they are all potentially infected. This is so whether the fracture is compounded from within or from without. All who have seen a number of compound fractures can recall tragic stories following a simple dabbing with iodine of the pinhole type of

compound fracture My associates and I have decided that all such fractures should be treated by the regular excision-debridement method

Again, there are a few cases of compound fractures in which the structures are so mangled and bones, muscles, vessels and nerves have been so obviously torn beyond repair that amputation is the only surgical solution These are the obvious cases There is a type, however, with which one too often lets an enthusiastic desire to save a limb overcome good surgical judgment In such cases one forgets the inevitable later virulent sepsis or the slow or nonestablished collateral circulation causing gangrene and infection, and one amputates too late This is not a plea for amputation as such It is a plea to the operating surgeon to counsel wisely with himself and others in such borderline cases He should and must remember the possible saving of life by primary amputation versus the temporary saving of the limb with a later inevitable amputation and probable loss of life from sepsis

Complications—Despite the conscientious and meticulous care given to compound fractures, the common enemy, sepsis, does appear and do damage in minor and major degrees Its therapy, therefore, must be given due consideration In some of our cases during the past two years we have been giving sulfanilamide as a prophylactic medicament to those patients in whose cases the initial culture showed some growth of streptococci The two less frequent but virulent and deadly types of sepsis are the gas bacillus infection and tetanus At the first sign of "gas" infection (the characteristic odor, loss of contractibility of the muscles when they are pinched with a forceps and their discoloration, pain, elevated temperature and pulse rate, crepitus, a tympanic area about the wound or the beginning of cutaneous mottling) specific treatment should be instituted at once

The original culture of material taken from the wound before its cleansing and debridement may give even earlier warning

My rules for the treatment of gas bacillus infection are as follows

- 1 Operate as soon as the diagnosis is made
- 2 Make the local preoperative preparation as rapidly as possible, avoiding all unnecessary trauma
- 3 Do not use tourniquets
- 4 Make long, deep incisions
- 5 Go between rather than through normal muscle fibers
- 6 Excise all tissue which appears infected
- 7 Sterilize the wounds as rapidly as possible with alcohol
- 8 Place Dakin tubes into the wound in advantageous places, and pack gauze strips saturated in hydrogen peroxide about them
- 9 Over all put sterile petrolatum gauze packs
- 10 Connect Dakin tubes to a common tube through which fresh diluted solution of sodium hypochlorite U S P (Dakin's solution) and

hydrogen peroxide can be injected alternately and which can be connected to an oxygen tank via a water bottle, so that between the irrigations with the sodium hypochlorite solution a fresh supply of oxygen is being constantly sent to the tissues

11 Use 100 cc doses of the specific anti-gas-bacillus serum daily or if deemed necessary at six hour intervals

12 Stimulate with care

13 Give frequent fractional blood transfusions

14 Record the pulse and temperature every half-hour

15 At the least sign of rapid spreading of infection or of increasing pulse rate and temperature, do a rapid guillotine or transfexion amputation and follow it with careful stimulation

16 Perform the enumerated steps as rapidly as you can

Tetanus, at least in this geographic area, is a rare complication today. However, when tetanus does appear we institute specific treatment at once. Our therapy follows along the general lines as laid down today. First, a careful intradermal test with the serum is given. If the result is positive, a most careful desensitization is done. One hour after this, an intravenous injection of 10,000 to 20,000 units is given subcutaneously and repeated at eight to twenty-four hour intervals until 200,000 units has been given. After this, an intravenous injection of 50,000 units is given. Twelve hours later the procedure is repeated. Today it is thought that massive doses should be administered as early as possible, not less than 100,000 units is advocated as an initial dose for all adult patients in whom the infection is not obviously mild. Even if symptomatic improvement occurs after large initial doses, the patient is given repeated doses of 50,000 to 100,000 units. It cannot be definitely concluded that intraspinal administration offers any advantage. It has also been found that dextrose (in vitro) is capable of neutralizing the tetanus toxin to a certain extent, and so in addition to the antitetanus serum, a daily 200 cc intravenous injection of 10 per cent dextrose is given. The wound is, of course, left wide open and treated hourly with hot dressings wet with diluted solution of sodium hypochlorite or through Dakin tubes by alternating hourly irrigations with the sodium hypochlorite solution and with hydrogen peroxide. In conjunction with this the patient is transferred to an isolated, darkened room. Everything movable that is not needed in the room is removed. The door must have rubber checks. The nurses must wear rubber-soled shoes. Morphine, allonal (allylisopropylbarbituric acid with aminopyrine) amytal or avertin with amylene hydrate must be used to keep the patient quiet. For convulsive seizures a general anesthetic may be used.

The virulent *Streptococcus haemolyticus* infection also gives us considerable worry and work. We give the patient subpectoral and intra-

venous injections of physiologic solution of sodium chloride and dextrose solution. In some cases we give whisky or brandy. Sulfanilamide or one of its newer derivatives is also given routinely in these cases. We also see that a well chosen diet is given. However, the most important therapy for this virulent type of infection is repeated fractional blood transfusions. We are firmly convinced that such transfusions, judiciously dosed and spaced, have saved many patients. These transfusions may range from 150 to 500 cc and can be of the citrated or of the whole blood type. A frequent check-up of the blood serves as a guide in regard to the frequency and time of the transfusions.

This treatment we give also for the serious *Staphylococcus aureus* infections. With all such infections we find that painstaking and alert special nursing is absolutely necessary for a happy outcome. Also, in cases of serious infection we confer with the internist in regard to the type of treatment. Our local treatment consists of adequate free drainage with active dakinization or frequent changing of hot moist dressings saturated with diluted solution of sodium hypochlorite, with hot flaxseed dressings over all. When extremities are involved, we make use of a specially wired bed cradle which is provided with electric bulbs to maintain an equitable warm temperature. We also make use of physical therapy, i. e., we give radiant heat by means of the infra-red lamp and also expose the patient locally and generally to ultraviolet rays. We usually put the patient into a suspension apparatus.

Despite this local radical surgical treatment giving adequate free tissue drainage, we have found that there is a certain type of compound fracture which is associated with a protracted elevation of temperature and a characteristic persistent pain. Fortunately such fractures are uncommon. The following case illustrates well the type to which I refer.

REPORT OF A CASE

In the spring of 1925 a girl 6 years of age was transferred to the Boston City Hospital from another hospital. Three weeks earlier she had sustained a most severe compound fracture of both bones of the lower part of the leg. She had been carefully and intelligently treated. The fracture had been treated from the beginning by the "open" method. It was well dakinized with diluted solution of sodium hypochlorite. Despite the careful treatment, sepsis crept in, and during the third week it was at its height. On two occasions well planned incisions and drainage operations were performed, yet the fever, the heightened pulse rate and the pain persisted. It was at this stage that she was transferred to the Boston City Hospital. The previous drainage of the soft parts was obviously inadequate, so infection of the bone was the only possible cause of local pain. Therefore, the fractured ends of the bones were guttered and pus was found. Because of overriding, the ends were separated and held in Smith clamps in the reduced position. The wound was dakinized.

The child had immediate relief from pain after this operation. In fact, she had a remarkably smooth, uneventful convalescence. There was no marked seques-

tration In six weeks, with good callus formation present, the Smith clamp was removed, in another six weeks the wound was clean and healed. The fracture was in excellent position and well united. Today the patient is about 21 years of age, and her injured leg is as long and straight as the other one and functions perfectly.

Cases like this showed us that compound fractures associated with persistent fever and pain despite apparently good tissue drainage need adequate bone drainage. I may also say here that, although we are not so enthusiastic as Baer was about his maggot therapy for acute uncomplicated osteomyelitis, I can truthfully say that for cleaning up obstinate, chronically septic compound fractures with the complicating osteomyelitis the Baer maggot therapy has proved very satisfactory to us.

Delayed Union and Nonunion—There are two other annoying complications, and they are of great importance, especially economically. These are delayed union and nonunion. It is the general rule that compound fractures unite slowly and occasionally not at all. Because of this, one must give most of the patients specific medicine and diet (cod liver oil, viosterol in oil and so forth), as well as physical therapy (diathermy, ultraviolet irradiation, massage). Selected patients are given indirect stimulation by weight bearing with fitted ambulatory splints or properly prepared plaster of paris casts with Boehler walking irons or plaster soles and heels.

However, despite all this local and general specific treatment, there are occasional cases of obstinately delayed union in which the bone apparently will take many months to unite or to go to an ultimate state of nonunion. From our actual experiences with such cases my associates and I have come to the conclusion that the patients can be saved economically valuable months by some simple, stimulating bone-forming operation, such as the modern adaptation of Dr. Daniel Brainerd's hole drilling or that procedure plus an inlay graft, chip grafts or an osteoperiosteal graft. The great saving of time to the patient, insuring him a return to normal work and wages so much earlier, is a vital economic argument for this procedure.

SUMMARY

Intelligent first aid should be given in cases of compound fractures. This includes proper handling, modern emergency splinting and careful transportation.

In cases of compound fracture it is absolutely imperative to consider first, the patient and, second, the fracture. One should be prompt in giving proper rest, stimulation, prophylactic injections of anti-gangrene and antitetanus serum and general supportive treatment with

an emergency dry sterile dressing and external traction and splinting. One should also be careful in the general examination to look for signs and symptoms of internal damage.

To insure good teamwork it is necessary to have well planned methods of preparation of the skin, debridement and cleansing of the wound. In treatment of the fracture itself, it is urged that surgeons be open minded. One should "size up" the situation quickly and be ready to use any of the several universally accepted methods for traction, internal fixation and other therapeutic measures.

One should not be dogmatic about "closed" and "open" wounds. One should be ready to use either the closed or the open technic according to one's judgment.

The type of external fixation should be chosen carefully.

One should counsel wisely and with others as to the question of primary amputation versus probable later amputation for complicating virulent sepsis with its probable fatal result.

In the treatment of late complicating gas bacillus or tetanus infection, one should give prompt and radical treatment with appropriate stimulation and supportive medical measures. The same may be said of the virulent streptococcic and staphylococcic infections.

One should consider bone grafting as a valuable time saver in carefully chosen cases of delayed union.

HIGH CHROMIUM, LOW NICKEL STEEL IN THE OPERATIVE FIXATION OF FRACTURES

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The purpose of this paper is to report the experimental and clinical use of high chromium, low nickel steel in the operative treatment of fractures in the service of Drs. William Dairach and Clay Ray Murray. The reason for the choice of this material derives from some of the difficulties encountered in the use of other metals as well as from the guiding work of Zierold,¹ who studied the interaction between a series of metals and living tissue, and of Jones and Lieberman,² who concluded that a high chromium, low nickel alloy is least objectionable for internal fixation.

Aside from the cases in which for mechanical or other reasons the operative method of treatment of fractures has failed, there has accumulated in this and other clinics a group of cases in which the plate or screws used in the mechanical fixation of the fractured bone have broken. The breaking of a vanadium plate or screws in such instances is a failure in treatment and sometimes a surgical tragedy.

In the face of these difficulties it is not easy to defend the operative treatment of fractures. However, a defect or a failure in method does not invalidate a principle, nor does a good principle justify a hopeless method. But because my associates and I believe that the operative method for the treatment of fractures is justified under controlled circumstances,³ we seek to improve the method and reduce the hazard of accidental failure.

METALLURGIC CONSIDERATIONS

From extended clinical experience it became obvious that the vanadium alloy failed in certain respects. There are many cases in which it is necessary to remove the metal used for fixation because

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1 Zierold, A. A. Reaction of Bone to Various Metals. *Arch. Surg.* 9: 365 (Sept.) 1924.

2 Jones, L., and Lieberman, B. A. Interaction of Bone and Various Metals. Vanadium and Rustless Steel. *Arch. Surg.* 32: 990 (June) 1936.

3 Murray, C. R. Primary Operative Reduction of Fractures of Long Bones as a Method of Choice. An Evaluation of Principles read before the Section on Orthopedic Surgery of the American Medical Association. St. Louis, May 19, 1939. to be published.

of evidence of local irritation, pain and absorption of bone around the metal. At removal there are corrosion of the plate or screws, unhealthy tissue granulation and even exudate, which, when examined by the usual bacteriologic methods, proves to be sterile. This is apart from the cases in which there is failure of internal fixation or of the plates or screws. In fact, susceptibility to corrosion has been used to explain the breaking of the metal.

Not is this all. Those who champion the operative method have had to deal as well with an old prejudice—a prejudice which may have considerable foundation but which, with the use of better methods, surgeons may outgrow. In this service it is considered good surgery to place foreign bodies in tissue or even in compound wounds if it contributes to fixation of fractures and therefore reduces spread of infection (Darrach⁴). However, this departure from an accepted method is not easy to defend. Experience shows that vanadium alloy is frequently unable to withstand the oxidizing, reducing and electrolytic⁵ influence of tissue juices. Particularly is this true in cases of compound fractures which have gone on to infection. However, infection is not the important factor, because absorption of bone and the other changes previously mentioned can take place in a perfectly clean wound.

The blame for its shortcomings cannot be placed on the vanadium alloy. An important factor has been that, though the preparation is standardized, the quality of the plates put on the market cannot be controlled. This was proved conclusively when plates of various origins were tested for resistance to minute vibratory stresses not surpassing the elastic limits of the steel⁶. Many plates subjected to 3,000,000 to 5,000,000 vibrations appeared in crude test to be just as tough afterward as before, whereas others became so brittle that they could be snapped by hand. This was not true of the high chromium, low nickel alloy plates similarly tested. In fact, they seemed less ductile but tougher (i. e. to crude twisting and bending deformations) and yet not brittle.

These defects have been investigated by others, and some of the causes have been attributed by Martin⁷ to several sources.

The failure of bone plates and screws can be traced to methods of manufacture that are not in compliance with the Commercial Standards CS37-31, Bureau of Standards U. S. Department of Commerce. The methods employed are such

4 Darrach, W. Treatment of Compound Fractures, Surg. Gynec. & Obst. 66:815, 1938.

5 Venable, C. S., Stuck, W. G. and Beach, A. The Effects on Bone of the Presence of Metals Based on Electrolysis, Ann. Surg. 105:917, 1937.

6 Fulton, J. F. Muscular Contractions and Reflex Control Movement. Baltimore: Williams & Wilkins Company, 1926.

7 Martin, D. I. Personal communication to the author.

that both the bone plates and the screws were of unsound design from an engineering point of view. Sharp corners at the bottom of the screw holes in the various plates provided sections subject to enormous stress concentration, from which failure invariably started. Excessive depths of the centering holes in the screw heads produced sections of extreme weakness when the centering holes entered the threaded sections of the screws. Failure of screws occurred in these sections.

In addition to the mechanical faults noted above it is felt that the hardness and chemical composition set forth in CS37-31 are not the most desirable for the purpose. It would seem that certainly a softer material, and, perhaps, even one of different chemical composition, would better serve the purpose of these parts.

Cases have been observed in this clinic in which the vanadium steel plate was broken postoperatively and after bony union had taken place. That is, the length of time during which the plate was in the body did not seem to be a decisive factor. In other words, it may be doubted that the break took place as a result of prolonged electrolytic corrosion or, on the other hand, because of fatigue failure. The most likely explanation involves both factors and adds that the plates were essentially defective as a result of the manufacturing process. The following illustrative data were culled from the operative records:

Patient D R, fracture of the shaft of the tibia, broken plate discovered on the first postoperative day, while the fracture was in suspension.

Patient M D, fracture of the radius, broken plate discovered eight days after the operation, with the fracture in a "sugar-tong" splint.

Patient S S, compound fracture of the femoral shaft, broken plate discovered twenty days after the operation, with the fracture in suspension.

Patient M S, fracture of the femoral shaft, broken plate discovered twenty-two days after the operation, with the fracture in suspension.

Patient T D, fracture of the radius and ulna, broken plate discovered five weeks after the operation, with the fracture in a "sugar-tong" splint (plate used on the radius only).

Patient M P, fracture of the femur, broken plate discovered sixty-two days after the operation, while the patient was moving the leg in a brace.

Patient C S, fracture of the femur, broken plate discovered thirteen days after the operation, with the fracture in a tubular plaster splint.

REASONS FOR THE USE OF HIGH CHROMIUM, LOW NICKEL STEEL

In choice of materials for experimental and clinical use my associates and I were guided chiefly by the work of Zierold, who reported the adverse influence of certain metals, including nickel, on bone healing but cited the relatively inert nature of stellite. This work was extended by Jones and Lieberman, who considered not only the relation of the material to the tissues but that of the tissue juices to the material. Since that time the advent of high chromium low nickel steel on the com-

mercial market at a relatively low cost and the increase in knowledge of handling the material have recommended it for use. Unlike vanadium, the American product is easily available, and its composition and preparation are subject to careful control.

The material used was produced by the Crucible Steel Company of America and fell into the Rezilal KA2 and FM188 groups. These are trade designations for the austenitic group of alloys recommended⁸ for their properties of resistance to corrosion.

Chemical Composition—The composition of the alloy in percentage, according to a bulletin of the Crucible Steel Company, is as follows:

Chromium	17-19
Nickel	8-9.5
Carbon	0.7 maximum
Phosphorus	0.1 maximum
Sulfur	0.15 maximum
Molybdenum and selenium	optional

Physical Properties—As reported in the Crucible Steel Company's catalog, some of the physical properties of the alloy are:

Tensile strength	85,000 to 95,000
Yield point	30,000 to 40,000
Elongation in 2"	55 to 60%
Reduction of area	65 to 75%
Brinell	130 to 170
Charpy	100
Thermal conductivity (gram calories per cubic centimeter, per second, per degree Centigrade)	0.052
Specific gravity	7.94
Specific heat	0.118
Melting point (deg. F.)	2,550
Specific electrical resistance (microhms per cubic centimeter)	
20 deg. C	73
100 deg. C	90
500 deg. C	106
800 deg. C	111
Coefficient of linear expansion (per degree Centigrade)	
0 to 100 C	0.000016
0 to 600 C	0.000018
0 to 1,000 C	0.000020
Modulus of elasticity	28,000,000 to 30,000,000

There are several conditions in the manufacture and finishing of the steel which have important bearing on its behavior. Cold working

⁸ Bergen, L. S. Personal communication to the author.

markedly increases the "Bimell," or relative hardness, and makes the metal less ductile. This has also some relation to the contour of the grain and distinctly reduces resistance to corrosion. Cutting, drilling, milling and threading must be done with lapped tools with a smooth, sharp cutting edge and with adequate clearance to minimize the "tearing" which can occur in the soft state. The final surfacing of the steel is extremely important. It should be polished and buffed with a non-ferrous material and afterward passivated by immersion in 20 per cent nitric acid at 65 C for a half hour to give, theoretically, a molecular chromic oxide coating. Great care should be exercised to remove whatever fragments or microscopic grains of non-ferrous steel may be left in the surface as a result of machining.

These processes are carried out to reduce to the minimum foci for electrolytic corrosion. If properly handled, the material should be practically noncorroding even in the presence of infection and electrolytically inert in tissue fluids. It should have a fair degree of ductility, which makes it possible to form it to the contour of the bone. Although its tensile strength is not so great as that of the vanadium alloy, it is adequate to the needs, and in experimental work and clinical surgical application by other members of the staff as well as by myself in 98 consecutive cases I have yet to discover failure because of the metal itself. In clinical use I have found that the presence of the steel, even in compound wounds in which the metal is exposed to the external atmosphere, does not inhibit osseous repair. In fact, if the devices (plates or screws) are not too superficially placed, granulation tissue will cover them, and it is possible to pinch graft regions of loss of soft parts and skin.

USE OF THE FIXATIVE APPARATUS

The scope of this paper does not cover the importance of organization of a fracture service³ in the successful treatment of fractures and takes for granted the use of a meticulous nontouch surgical technic. But there are many details in the application of technic which bear directly on the effectiveness of a method.

The first condition for successful use of the operative method is adequate surgical exposure. It may be added that although exposure is relatively simple in the superficial tibia and ulna it is better to place the plate and screws deep in soft tissue rather than near the skin. In compound fractures it may be expedient to depart from this rule, but in such a departure secondary removal of the device used for internal fixation is frequently necessary.

With good exposure the second necessary condition may be more easily accomplished, i. e., anatomic reduction. This implies thorough

study of the roentgenograms before operation and familiarity with the use of bone-holding forceps. But reduction is not enough. That the third condition may be fulfilled, holding the reduction during fixation is a prime requisite. This must be done with a minimum of periosteal stripping. If the periosteum is stripped or extensively torn, it should be removed in part to eliminate it as a potential barrier to revascularization of the cortical bone.

The most important condition to be fulfilled is adequate rigid internal fixation. This is not always easy. The presence of multiple fragments may make internal fixation very difficult and sometimes impossible. However, in a usual case the following points should be borne in mind:

- 1 The plate must be formed to fit the contour of the bone by gentle use of small bending irons.
- 2 The plate should be held to make possible the accurate placement of drill holes, these being vertical to the long axis of the bone.
- 3 The drill used should be the size used in machine practice, the thread tap being fitted to the proper screw.
- 4 The hole must be bored with a sharp drill with good clearance and in true line to avoid reaming the hole and making it large for the cutting screw, thus producing a "sloppy" fit.
- 5 The self-tapping screw when driven must be in the exact line of the drill hole to engage the opposite cortex when that is sought.
- 6 When all the screws are in place, they should be "snugged up" firmly but not roughly to take out all play between the bone and the plate and plate and the screws. Stripping of the thread in the bone, however, should be avoided.
- 7 The screws must be so placed as to avoid injuring the thread against the plate.
- 8 The plate must be long enough to clear the fracture site and in proportion to the length of the fracture and of the bone.
- 9 It is of the utmost importance to place one or more separate oblique screws crossing the fracture and vertical to the screws fastening the plate to take up the torque stresses invariably present.
- 10 When possible, it is wise to engage both cortices. Particularly is this true in the presence of a deep-lying loose fragment.

TISSUE REACTION

Observations were made of the reaction of tissues to the material under discussion.

MATERIAL AND METHOD

Mature dogs were used for observation of the behavior of high chromium low nickel steel in living tissue. It seemed unnecessary to repeat the work of Jones and Lieberman in the *in vitro* experiments. The use of screws not taking

any stress of function appeared too limited in application. Accordingly, small screws and plates were made and put into dogs just as in the clinical operative treatment of fractures. At operation one of the long bones to be plated was fractured with a chisel or a bone-cutting forceps or both. The fracture was reduced and fastened with four screw plates, such as are now used to repair small bones of the forearm or metacarpal bones. The screws were self tapping, with a sharp cutting edge (figs 1 *B* and 6). A special screwdriver giving rigid control of the screw in rotation and long axis (fig 1 *A*) and a modified nontouch technic were used throughout.

The plates and screws were fabricated (fig 2) by the special methods employed for this type of metal. After fabrication they were carefully cleansed in soap

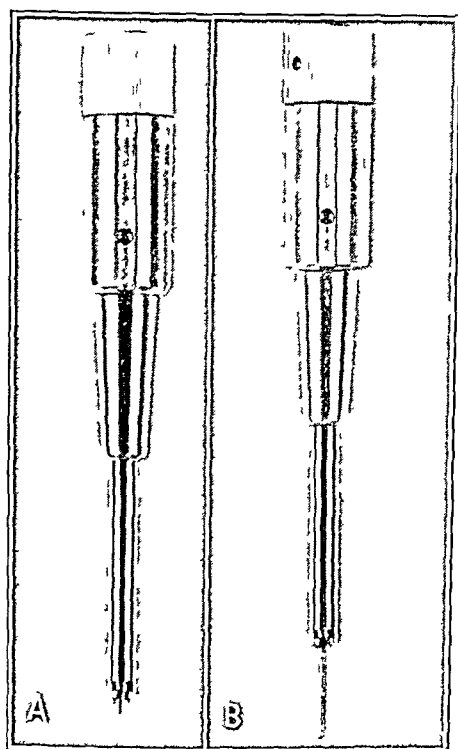


Fig 1—*A*, screw driver designed and perfected by Mr Joseph Becker, of the department of pharmacology, College of Physicians and Surgeons, Columbia University, with a knurled head driven home and used as an ordinary driver. *B* same driver with the screw in position and gripped.

and water, alcohol and ether. They were desiccated in an oven for twelve minutes to one-half hour at 112 C and over calcium chloride for twenty-five minutes and were then weighed.

The animals were killed at different periods up to two years. The shortest period for which the metal remained in place was two days. This was in the first animal, which was operated on soon after arrival from out of town. It died postoperatively of bronchopneumonia.

PROTOCOL FOR AN ANIMAL KILLED AT TWO DAYS

Dog 1—A brown and white pointer bitch weighing 152 Kg was used. Osteotomy of the right radius was performed, with a plate and screws. On Dec 2, 1936, preparation was made with soap, water, alcohol, ether and iodine. The anterolateral approach was used. Towels were fastened to the skin with clips. Anesthesia (ether) was induced by the open method. The periosteum

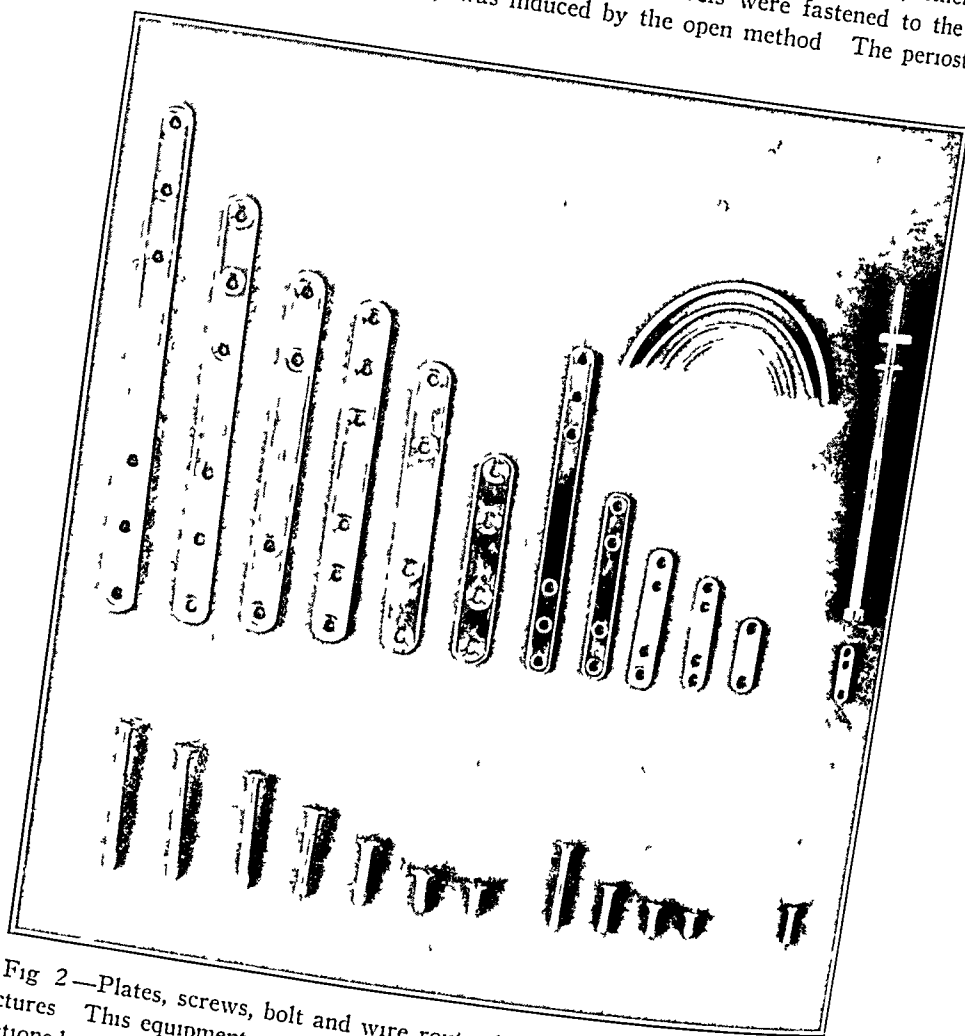


Fig 2—Plates, screws, bolt and wire routinely used in the operative fixation of fractures. This equipment is made and marketed by Mr Joseph Becker, previously mentioned.

was stripped. The radius was broken with a flat osteotome. A no 41 drill, a no 10 plate and four screws (nos 1, 9, 6 and 7) were used for fixation, which was rigid. The wound was closed in three layers. On December 3 there was a good deal of edema. The breathing was labored and irregular. Early pneumonia was present. There was no tension on the sutures. The dog could touch the foot to the ground.

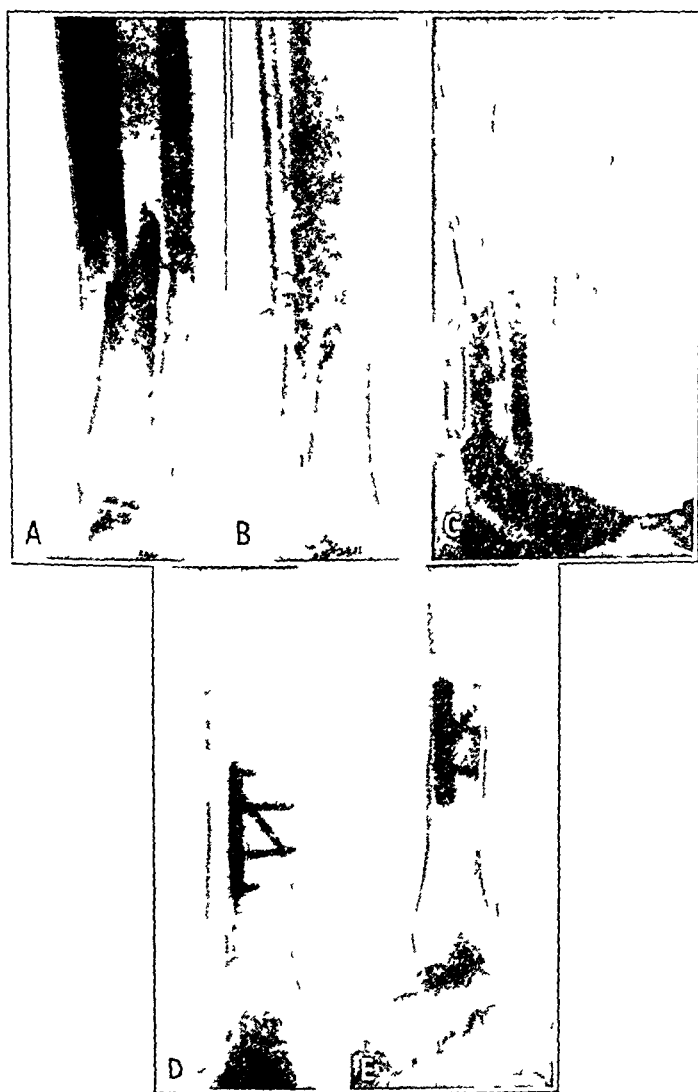


Fig 3—A, preoperative film of a compound fracture of the right tibia B, another projection C, roentgenogram taken on the first postoperative day, with the fracture in suspension D and E show appearance nine months after operation

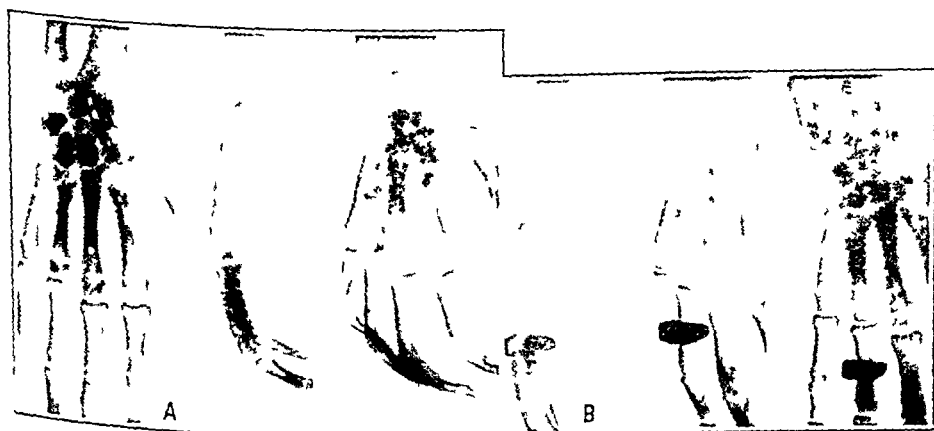


Fig 4—A, preoperative film, and B, film taken nine months after operation The films illustrate the use of the metal in fractured metacarpal bones

The animal died early in the morning of December 4 Extensive consolidation of the right lung and some consolidation of the upper lobe of the left were noted There was a film of coagulum over the plate and screws in the right radius

The following data were recorded

No 10 plate	1 1897 Gm at operation
	1 1891 Gm at removal
	<hr/> 0 0006 Gm loss
	0 06 per cent loss
No 1 screw	0 2903 Gm at operation
	0 2895 Gm at removal
	<hr/> 0 0008 Gm loss
	0 2 per cent loss
No 6 screw	0 4876 Gm at operation
	0 4876 Gm at removal
	<hr/> 0 0000 Gm loss
	0 00 per cent loss
No 7 screw	0 4556 Gm at operation
	0 4554 Gm at removal
	<hr/> 0 0002 Gm loss
	0 004 per cent loss
No 9 screw	0 2904 Gm at operation
	0 2898 Gm at removal
	<hr/> 0 0006 Gm loss
	0 2 per cent loss

PROTOCOL ON AN ANIMAL KILLED AT FORTY-NINE DAYS

Dog 13—A dark spotted hound weighing 16 5 Kg was used Osteotomy of the right radius was performed, with application of a plate and screws, on Dec 16, 1936 The usual aseptic technic was employed Ether anesthesia was induced by the open method The anterolateral approach was used Rigid fixation was obtained by means of a plate (no 10) and four screws (nos 1, 7, 6 and 9) These appliances were from a new batch

On December 21 the leg bore weight The dog was lively There was some redness about the wound

On Feb 3, 1937, the dog ran well, with good use of the foot Roentgenograms were taken, and the dog was killed The proximal two screws were covered with dense fibrous tissue which separated easily from the plate The distal part of the plate and the distal screws were almost completely covered with dense bone. In the groove of the head of the most distal screw (no 9), bony tissue was present, all screws were removed with difficulty The screws and plate appeared smooth and shining, there was no evidence of corrosion The tissue about the plate was pinkish white The fracture line was well healed and slightly paler than the tissue nearby

The following data were recorded:

No. 10 plate	12154 Gm. at operation 12143 Gm. at removal <hr/> 00011 Gm. loss 008 per cent loss
No. 1 screw	02874 Gm. at operation 02875 Gm. at removal <hr/> 00001 Gm. gain 003 per cent gain
No. 6 screw	04695 Gm. at operation 04697 Gm. at removal <hr/> 00002 Gm. gain 004 per cent gain
No. 7 screw	04478 Gm. at operation Loss of weight in removal not used
No. 9 screw	02768 Gm. at operation 02771 Gm. at removal <hr/> 00003 Gm. loss 01 per cent gain

PROTOCOL ON AN ANIMAL KILLED AT ONE HUNDRED AND NINETY-SIX DAYS

Dog 8—A mixed "collie mongrel" bitch weighing 15.3 Kg. was used. Osteotomy of the right tibia was done, with application of a plate and screws, on Jan. 6, 1937. Soap, water, alcohol, ether and iodine were used in preparation. Ether anesthesia was induced by the open method. The anterolateral approach to the right tibia was used. Osteotomy was done at the junction of the upper and the middle third. The periosteum was stripped. The fracture was reduced and fixed with a plate (no. 10) and four screws (nos. 1, 7, 9 and 6).

On January 7 there was some edema of the leg and paw. There was a suggestive cough. The dog was friendly.

On January 8 the dog was in good spirits and ate well. More edema was observed. The wound was clean.

On July 21 the dog was killed. The no. 9 screw was removed with great difficulty. It was injured, with loss of weight. The no. 6 screw was so well healed in that the tip broke.

The following data were recorded:

No. 10 plate	25458 Gm. at operation 25445 Gm. at removal <hr/> 00013 Gm. loss 02 per cent loss
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Fig 5—Complicated subtrochanteric fracture of the left femur, before operation (A) and after union had taken place (B)



Fig 6—Section of the broken screw tip (no 6 screw) in dog 8, killed at 196 days. The photograph is a magnification approximately 50 times of the screw tip embedded in bone tissue. Note that one half of the metal shows its granular surface, the other half is covered by bone substance, which has healed into the recess which bounds the sharp self-tapping threads. The photomicrograph was taken with combined transmitted and reflected light. Hematoxylin and eosin stain.



Fig 7—Another screw hole (same animal as in figure 6) showing the survival of bone tissue in the grooves of the screw threads. Approximate magnification, $\times 12$. Hematoxylin and eosin stain.



Fig 8—Section of a dog's radius in the long axis of the screw hole. Note the ridges which represent bone tissue of the thread approximating the screw. Approximate magnification, $\times 50$. Hematoxylin and eosin stain.

No 9 screw	0 4824 Gm at operation
	0 4807 Gm at removal
	<hr/> 0 0017 Gm loss of weight, not not counted, screw injured 0 3 per cent loss of weight
No 7 screw	0 4776 Gm at operation
	0 4771 Gm at removal
	<hr/> 0 0005 Gm loss 0 1 per cent loss
No 1 screw	0 4795 Gm at operation
	0 4792 Gm at removal
	<hr/> 0 0003 Gm loss 0 06 per cent loss
No 6 screw	0 4902 Gm at operation, Broken
	at removal, used for section

PROTOCOL ON AN ANIMAL KILLED AT THREE HUNDRED AND SIXTY-SIX DAYS

Dog 14—A black and white spotted hound weighing 17 4 Kg was used After the usual preparation, osteotomy of the right radius was done, with application of a plate and screws, on Dec 3, 1936 With the dog under ether anesthesia induced by the open method the right radius was exposed through a muscle-separating anterolateral approach Towels were held on the skin with clips The periosteum was stripped, and a fracture was made with a large osteotome A no 41 drill was used for the screw holes A no 11 plate (four holes) and four screws (nos 2, 4, 5 and 3) were used The no 2 screw and the no 3 screw engaged one cortex only, the no 4 screw and the no 5 screw engaged both cortices Rigid fixation in good position was obtained The wound was closed in three layers

On December 5 the animal was lively There was not much edema The dog did not use the paw

On December 9 there was no weight bearing

On December 16 the leg bore weight and the wound was healed

On December 21 the dog was in excellent condition

On December 4, 1937, the animal was killed The skin was healed, the muscle planes were healed The plate and screws were covered with a thin, fibrous membrane, through which the plate shone

The following data were recorded

No 2 screw

Short very difficult to remove,
may have lost substance in
process of removal

0 2971 Gm at operation

0 2960 Gm at removal

0 0011 Gm loss

0 3 per cent loss

No. 3 screw	Short, difficult to remove 0.3021 Gm. at operation 0.3014 Gm. at removal <hr/> 0.0007 Gm. loss 0.2 per cent loss
No. 4 screw	Long, impinged on ulna, easy to remove, friable tissue beneath plate at screw site 0.4675 Gm. at operation 0.4670 Gm. at removal <hr/> 0.0005 Gm. loss 0.1 per cent loss
No. 5 screw	Long, moderately difficult to remove 0.4773 Gm. at operation 0.4765 Gm. at removal <hr/> 0.0008 Gm. loss 0.1 per cent loss

PROTOCOL ON AN ANIMAL KILLED AT TWO YEARS AND ONE MONTH

Dog 12—A brown and white spotted hound bitch weighing 16.6 Kg. was used.

On Dec. 9, 1936, osteotomy of the right radius was done, with application of a plate and screws. The lateral approach was developed to the proximal and middle third of the right radius. Towels were used on the skin. The periosteum was stripped with a blunt elevator, and the fracture made with a bone-cutting forceps and an osteotome. The fracture was reduced and held. A no. 41 drill was used for holes. A screw plate and four screws were used for fixation, which was fairly rigid. The incision was closed in the muscular and aponeurotic planes with interrupted silk sutures. The skin was closed as well.

On December 16 the leg bore weight. The wound was healing. There was very little edema.

On Jan. 21, 1937, the wound was healed. The leg bore weight. There was no edema.

On June 25 there was periodic development of a sinus at the upper limit of the scar, with rehealing. The plate was palpable. The animal was active. The leg bore full weight.

On June 2, 1938 it was noted the sinus occasionally still reopened. The animal bore a litter of pups. The plate was palpable. The upper end of the plate was loose. Rotation of the leg was painless.

On Jan. 9, 1939 the animal was killed. Pronation and supination of the injured leg were equal to those observed on the other side. There was no frank exudate. The sinus did not go to the plate. The plate was loose at the upper end. The proximal three screws were removed with ease. The distal screw was fairly firm. The plate and screws were completely covered with a fibrous envelope.

The following data were noted

No 11 plate	1 1891 Gm at operation 1 1870 Gm at removal <hr/> 0 0021 Gm loss 0 1 per cent loss
No 1 screw	0 2895 Gm at operation 0 2890 Gm at removal <hr/> 0 0005 Gm loss 0 1 per cent loss
No 6 screw	0 4876 Gm at operation 0 4869 Gm at removal <hr/> 0 0007 Gm loss 0 1 per cent loss
No 7 screw	0 4554 Gm at operation 0 4547 Gm at removal <hr/> 0 0007 Gm loss 0 1 per cent loss
No 9 screw	0 2898 Gm at operation 0 2890 Gm at removal <hr/> 0 0008 Gm loss 0 2 per cent loss

OBSERVATIONS ON THE CLINICAL USE OF HIGH CHROMIUM, LOW NICKEL STEEL

The lack of evidence of electrolytic corrosion or loss of weight of the screws and plates in animals encouraged its use clinically. Well over 100 patients have been treated since the fall of 1936 with operative fixation. This was done by various members of the staff of the fracture service. Forty-two cases observed in 1937 and 53 observed in 1938 are considered here, not to evaluate them clinically or for end results but to extend observations on the use of the particular metal in question.

In 1937, 41 fractures were treated with fixation by the high chromium, low nickel steel plates and screws. Of these, 10 were humeral, 11 tibial, 8 femoral, 6 ulnar, 3 combined tibial and fibular with separation of the mortise, 2 radial and 1 acetabular.

Of the 41 cases, plates and screws were removed in 12. There were 6 compound injuries from which the plates and screws were removed. Four were fractures of the elbow with superficial plates, 1 a tibial fracture with a superficial plate and a persisting sinus and 1 a supracondylar fracture of the femur in which fixation was insecure and the plate and

screws were easily accessible. Of the 6 clean fractures from which the steel was removed fixation was insecure in 1. One case may be excluded on the basis that a wire of dissimilar composition had to be used to secure the coronoid process in a complicated fracture of the elbow. From only 1 of the fractures operated on not compounded and adequately fixed was the fixative apparatus removed. This was a fracture of the mid-shaft of the femur, fractured six months before and treated nonoperatively elsewhere. The femur was fixed on Aug 14, 1937. Five months after operation and one month after discarding the walking brace the patient noticed a mild ache at the site of operation. Seven months after operation a suture was expelled at the lower limit of the scar. A sinus persisted, and the plate was removed on June 20, 1938. Culture of material from the sinus showed *Staphylococcus albus*. At operation the tissue at the lowermost screw showed a brownish black granular discoloration. The culture was sterile and the operative site did not connect with the sinus tract.

In the 53 cases with 57 bones treated operatively in 1938 and considered here, there occurred 11 fractures of the humerus, 12 of the tibia, 6 of the ulna, 10 of the radius, 5 of both the tibia and the fibula with separation of the mortise, 5 of the metacarpal bones, 1 of the phalangeal bones and 7 of the femur. Six were compounded wounds. From 2 of the last-mentioned fractures the plates and screws were removed after bony union because of persisting sinuses. One was a tibial fracture in which the plate had been superficially placed for expediency. The other was a femoral fracture operated on ten days after injury and treated elsewhere with debridement and closure of the wound. Both progressed to bony union, although a sequestrectomy was required before the femoral fracture wound healed. The 4 compound fractures from which the steel was not removed but which healed were 2 ulnar injuries, 1 tibial fracture and 1 metacarpal fracture.

Of the 6 clean fractures from which the plates and screws were removed, 3 showed insecure fixation with partial pulling out of screws (2 femoral fractures and 1 ulnar fracture). From 1 metacarpal fracture the plate and screws were removed incidentally to the removal of a painful spike of bone which persisted after the fracture had healed. Two clean tibial fractures from which the plates were removed, though the fixation was secure, showed clinical evidence of irritation. Both had been treated with materials which were not properly prepared. That is, the plate and screws had not been buffed and passivated, because production had changed from a handicraft basis to machine production. From 1 of these the plate and screws were removed five months after operation, from the other, ten months after operation. There was definite evidence of tissue irritation. Foci of corrosion were found along the

thread grooves of the screws or in the shank of the screw, where the finishing turn of the threading tool had left a small recess in which foreign materials collected. The only plate that showed corrosion was one in which the corroding screw shank was in contact with the screw hole. Some corrosion also occurred in screws which were driven off center, the threads being partially stripped against the plate hole.

In recapitulation of the clinical use of high chromium, low nickel steel, the following data may be noted. Of the 98 bones operated on and fixed internally, removal of the fixative device was attributable to the steel itself in 3. In all 3 the material had been improperly prepared. With the 21 other bones from which the steel was removed either for lack of rigid fixation or in the presence of a compound wound or infection, corrosion was a negligible factor in removal.

It is interesting that in 1937, except for 2 tibial fractures in patients who died of other injuries, the fixation material was removed eventually from all compound injuries, i. e., in 6. Of the 6 compound fractures observed in 1938, the wounds healed over the plates and screws in 4.

SUMMARY

A high chromium, low nickel stainless steel alloy has been used experimentally in dogs and clinically for internal fixation of fractures.

Certain adverse factors found in its use are discussed.

Some technically primary requisites are stressed.

CONCLUSION

When certain requirements are fulfilled, a high chromium, low nickel alloy is an adequate material physically, metallurgically and clinically for internal fixation of fractures.

SITUS INVERSUS TOTALIS AND DISEASE OF THE BILIARY TRACT

SURVEY OF THE LITERATURE AND REPORT OF A CASE

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Transposition of viscera has been recognized since the days of Aristotle (who recorded observations on 2 instances of transposed organs in animals), but it was not until 1600 A. D. that Fabricius described a case of reversed liver and spleen in the human being.¹ Petrus Servius recorded a case of transposition of the viscera in 1615,² and Kuchenmeister (1824) first recognized the condition in a living person.³ Subsequent to this clinical pioneering, sporadic cases were reported throughout the literature, but the true incidence was not appreciated until the modern era began, in 1897, with Velssemeyer's³ demonstration of transposition by means of the roentgen rays. This mode of examination has made confirmation of the anomaly relatively simple, and the incidence of reported cases has increased accordingly. Cleveland,⁴ in 1926, found approximately 400 cases of transposition in the literature, and Larson⁵ estimated that there have been 75 cases reported since that time.

There is considerable variation in the frequency of this anomaly as reported by different authors. Thus, Sherk² reported 10 instances in 347,000 registrations at the Mayo Clinic in the preceding twelve year period. Lewald⁶ observed the condition 29 times in roentgen examinations of the chests and gastrointestinal tracts of 40,000 patients. Cleve-

From the Department of Surgery of Vanderbilt University

1 Lineback, P. E. An Extraordinary Case of Situs Inversus Viscerum
Totals, J. A. M. A. 75:1775 (Dec. 25) 1920

2 Sherk, H. H. Total Transposition of Viscera, Surg., Gynec. & Obst.
35:53, 1922

3 Velssemeyer. Ein Fall von congenitaler Detriokardie, zugleich ein Beitrag
zur Verwerthung der Rontgenstrahlen in Gebiete der inneren Medizin, Deutsche
med. Wchnschr. 23:180, 1897

4 Cleveland, M. Situs Inversus Viscerum. Anatomic Study, Arch. Surg.
13:342 (Sept.) 1926

5 Larson, C. P. Situs Inversus with Other Congenital Anomalies, Canad. M.
A. J. 39:474, 1938

6 Lewald, L. T. Complete Transposition of Viscera, J. A. M. A. 84:261
(Jan. 24) 1925

land⁴ reported observing 1 example in 10,000 routine dissections, and Rosler⁷ recorded 3 observed in 22,402 autopsies. Adams and Churchill⁸ stated that situs inversus was diagnosed in the cases of 23 of a total of 232,112 patients admitted to the Massachusetts General Hospital, an incidence of 0.002 per cent of the hospital population. Balfour⁹ wrote that 51 cases of situs inversus have been encountered at the Mayo Clinic over a period of twenty-one years. Cockayne¹⁰ stated the ratio of males to females with complete transposition to be 32:27 and added that the condition has been reported as occurring in all races except the Australoid.

NATURE OF TRANSPOSITION OF THE VISCERA

Transposition of viscera may be either partial or complete. The complete form has often been thought of as a mirror image of the normal, left handedness, position of the testes, etc., being used as criteria. Cockayne's¹⁰ study, however, shows no greater incidence of left handedness in patients with situs inversus than in normal persons, and so it cannot be assumed that the central nervous system, or at least that portion concerned with the determination of manual dexterity, shares in the transposition. Actually, the condition is best thought of as an abnormal (sinistral) rotation of the thoracoabdominal viscera resulting in a reversal of the normal relations. For example, in complete transposition the anatomic arrangements are briefly as follows:⁴ The heart lies to the right of the midline, and its chambers are reversed, the apex being the right ventricle, from which arises the aorta. The aorta arches toward the right, giving off the innominate artery (which subsequently divides into the left common carotid artery and the subclavian artery), the right common carotid artery and the right subclavian artery. The great veins empty into the left atrium, whence the blood passes into the left ventricle, the pulmonary arteries, the pulmonary capillary bed, the pulmonary veins and the right atrium, respectively. The thoracic duct lies to the right and empties into the right subclavian vein near its junction with the internal jugular vein. The lungs are structurally reversed, the right being bilobed and the left trilobed. Intra-abdominally, the cardia lies to the right of the midline and the lesser curvature extends toward the left. The spleen is on the right, and the gallbladder and liver (with reversal of the normal lobular arrangement of the

7 Rosler, H. Beiträge zur Lehre von den angeborenen Herzfehlern, über die angeborene isolierte Rechtslager des Herzens, *Wien Arch f inn Med* 19:505, 1930.

8 Adams, R., and Churchill, E. D. Situs Inversus, Sinusitis, Bronchiectasis, *J Thoracic Surg* 7:206, 1937.

9 Balfour, D. C. Personal communication to the authors, 1939.

10 Cockayne, E. H. Genetics of Transposition of the Viscera, *Quart J Med* 7:479, 1937.

latter), on the left. The entire intestinal tract is reversed, with the cecum and appendix on the left and the sigmoid flexure of the colon in the right iliac fossa.

Partial transposition is known to occur in three main forms although gradations between the types are so common as to make definite classification difficult. Thus one may have partial transposition of both the thoracic and the abdominal organs, transposition affecting the abdominal organs alone or dextrocardia alone. In the last-mentioned condition the normal chambers of the heart are reversed as is the location of the organ.

The relation between the various forms of partial transposition and total transposition is imperfectly understood, although in many of the reported cases there were gradations toward the complete which would make one suspect that the differences are more apparent than real. That is, all of the changes may be the result of the same fundamental process, the chief difference being one of degree.

ORIGIN

The nature of situs inversus has aroused the curiosity of medical investigators since the time of its original description, and speculations as to its origin have run the gamut of medical imagination, from the supernatural views of Aristotle, who considered it a visitation from the gods,¹¹ to the more elaborate embryologic explanations of recent years. Many of the latter have little or no evidence to support them, and chief among these are the hypotheses based on the assumption that the location of the viscera is determined by the course of their blood supply or by variations in their hemodynamics during the formative period. We shall attempt to focus our attention on the more fundamental of the factual theories.

In general, variations from normal development may be thought of as arising either from causal elements inherited in the germ plasma or from changes in the environment of the fertilized ovum. Studies of the former (the genetics of transposition) have for the most part been confined to analyses of the families of persons with situs inversus, whereas study of the "acquired" form has consisted of attempts to produce developmental abnormalities through changes in the external influences which act on the embryo during its earliest stages. Confirmatory evidence has been collected by the advocates of both views, and this evidence will be briefly presented. It should be remembered that the exponents of the heredity theory have the tremendous advantage of being able to arrive at their conclusions as the result of study of

¹¹ Beck, C. Case of Transposed Viscera with Cholelithiasis Relieved by a Left-Sided Cholecystostomy, *Ann Surg* 29 593, 1899.

the condition in human beings, whereas the supporters of the theory that the condition is acquired must rely on evidence collected from their observation of lower forms. Deductions drawn from animal experimentation are, as is well known, not always applicable to the human being.

For many years the attention of workers has been drawn to the not infrequent occurrence of transposition in monsters. Since in double monsters one often exhibits complete or partial transposition, it has been suggested that situs inversus represents monozygotic twinning with absorption of the normal fetus. If this were the true mechanism, one would expect to find many identical twins with reversal of viscera. Wilder¹² studied this problem, and he found that, although double monsters often exhibit many different degrees of visceral transposition, duplicate twins have only a few minor integumentary reversals, such as "mirror imaging" of the fingerprints of particular fingers. He considered these mirror reversals of normal symmetry as vestigial remains of a more generalized transposition in early fetal life. Newman¹³ found reversal of tegumentary patterns in armadillo quadruplets and expressed the belief that the relatively greater tendency toward reversal seen in these animals (and in monsters) was due to their separation late in ontogeny, human identical twins separate early.

Spemann¹⁴ and Pressler,¹⁵ working separately with *Bombinator igneus* in the neurula stage, found that by surgically reversing a section of the medullary plate together with a portion of the roof of the primitive gut situs inversus could be produced in many instances.

Stockard¹⁶ was able to produce certain deformities by varying the environment of *Fundulus* eggs. His work was based on the assumption that a given species develops at a specific rate, which is probably dependent on the rate of protoplasmic oxidation in that particular species. Experimentally, this oxidative rate could be varied either by lowering the temperature or by decreasing the supply of available oxygen, by thus altering the rate during certain periods when there was marked inequality of growth in different parts of the embryo.

12 Wilder, H. H. Duplicate Twins and Double Monsters, *Am J Anat* 3 387, 1904.

13 Newman, H. H. Heredity and Organic Symmetry in Armadillo Quadruplets, *Biol Bull* 30 173, 1916, Experimental Studies of Asymmetry in the Starfish, *Patiria Miniata*, *ibid* 49 111, 1925, Studies of Human Twins, *ibid* 55 283, 1928.

14 Spemann, H. Ueber embryonale Transplantation, *Verhandl d Gesellsch deutsch Naturf u Aertzer*, 1906, p 189.

15 Pressler, K. Beobachtungen und Versuche über den normalen und inversen Situs Viscerum et Cordis bei Anurenlarven, *Arch f Entwicklgsmechn d Organ* 32 1, 1911.

16 Stockard, C. R. Structure and Developmental Rate, *Am J Anat* 28 115, 1921.

almost any type of deformity could be produced. The type of monster produced was dependent on the stage of embryonic development at which the inhibiting environment was applied and in general the greatest deformity developed in those organs in which growth was most rapid at the time of inhibition.

Newman¹⁷ studied the effects of low temperatures on the development of *Patiria miniata*. He found that "icing" before or during early cleavage resulted in a high incidence of twins. "icing" at the blastula stage produced an increase in the percentage of larvae showing reversed or right-handed symmetry and similar cooling at other developmental stages resulted in different but equally striking results. In his opinion, reversal of symmetry is simply the specific effect resulting from arrest of growth of the larvae at the blastula stage.

The heredity theory has been somewhat strengthened by observations on insects that rotation may be caused by a gene. Thus, Sumner and Huestis,¹⁷ working with a mutant of *Drosophila melanogaster* in which the tip of the abdomen was rotated counterclockwise, found that this was determined by a recessive gene in the third chromosome. Other investigators have found somewhat similar but different genes of rotation in this same species.

Cockayne's¹⁰ comprehensive study of a fairly large number of human families showed that "complete transposition of the viscera agrees with what is expected of a rare recessive character in its familial incidence and general distribution within a family, in its occurrence in both members of a pair of monozygotic twins whose parents are normal, in the high percentage of first cousin marriages that give rise to it and, insofar as can be determined, in the ratio of affected to normal children in fraternities." His analysis revealed that other developmental abnormalities, such as congenital heart disease, are more common in persons with transposition than among the general population and that this liability to defective development is much greater with partial than with total transposition. He concluded that complete transposition is inherited as a recessive character determined by a single autosomal gene, and in his opinion partial transposition is probably determined by the same gene. The higher incidence of associated anomalies results in the classification of this gene with the partially lethal group.

Adams and Churchill,⁸ in attempting to correlate these divergent findings, offered the suggestion that there may be two types of person with transposition of the viscera: the true mutant, in whom the tendency toward transposition is inherited as a recessive character, and the true monster, in whom the transposition is the result of external influences acting after fertilization. The former would be expected to

¹⁷ Sumner, F. B., and Huestis, R. R. Bilateral Asymmetry and Its Relation to Certain Problems of Genetics, *Genetics* 6: 445, 1921.

the cystocele and rectocele were performed. The record of this admission contains the first description of pain, which she said she had first experienced sixteen years previously, shortly before the delivery of her fifth child. This and many subsequent attacks had consisted of pain in the epigastrium which radiated to the right flank. Each attack lasted several hours, the pain was severe, but morphine was not required. Hematuria had never been observed during the attacks. She stated that in recent years the frequency of the attacks had increased. In addition, she complained of pain in the lower part of the abdomen, which was separate and distinct from that in the upper part. She returned to the outpatient clinic several months subsequently, stating that she had had difficulty in breathing and that she wished to have the goiter removed. A nontoxic adenoma of the thyroid was removed on June 29. After discharge, she returned to the outpatient clinic on a number of occasions because of pain and swelling of her legs and obesity. On June 15, 1939, she stated that she had had severe abdominal pain four days previously which was similar to that which she had had intermittently

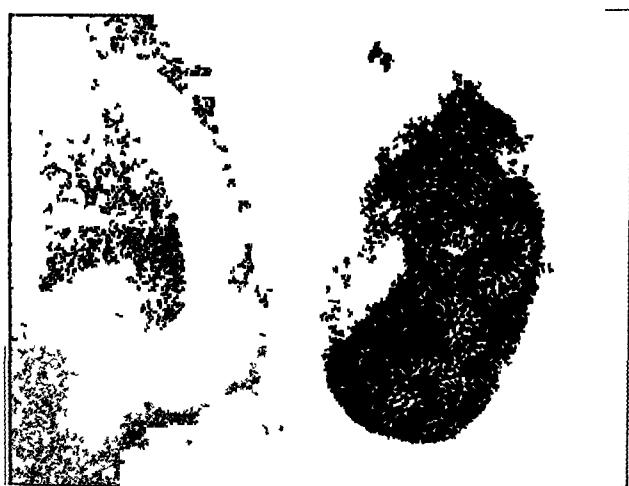


Fig 2—Postoperative roentgenograms of the gallbladder and appendix.

for sixteen years. The attacks were described as beginning with discomfort in the epigastrium followed by sudden sharp stabbing pains, usually in the right side of the epigastrium, with radiation to the right flank and to the back. The attacks were accompanied by severe nausea with eructation of gas and yellowish liquid but no frank vomiting. Jaundice had never been observed. Buttermilk and fried potatoes were the only foods which she had noticed as apt to bring on an attack. Intravenous cholecystographic examination showed good concentration of the dye and several opaque stones in the gallbladder, which was situated in the left upper quadrant of the abdomen (fig 1). Examination of the intestinal tract after a barium sulfate meal and a barium sulfate enema revealed no abnormality other than transposition.

With the patient under nitrogen monoxide, oxygen and ether anesthesia (endotracheal), operation was performed on July 13. A small paramedian incision was made, and the muscle was retracted laterally. Complete transposition of all the abdominal viscera was verified. The liver was almost entirely on the left, there being a thin layer of liver tissue on the right. The spleen was located just beneath the right side of the diaphragm. The appendix was in the left lower quadrant.

of the abdomen. It was removed, and the stump was inverted. There were many adhesions about the gallbladder which was slightly grayish and contained stones. There was scarring of the liver in the neighborhood of the attachment of the gallbladder. After the adhesions about the gallbladder had been freed, the organ was removed from below upward, the cystic duct and vessels being ligated separately. The common duct was not dilated. A cigaret drain was inserted, and the incision was closed. The gallbladder contained three rather large calcium, bilirubin and cholesterol stones. A roentgenogram (fig. 2) was taken of the gallbladder after removal.

The patient was discharged from the hospital sixteen days after the operation. She has returned to the outpatient clinic on several occasions for observation, and there have been no further complaints of pain or indigestion.

COMMENT

Reported cases of lesions of the biliary tract in association with situs inversus are few. A fairly comprehensive survey of the literature reveals only 17 reported as such, and in several of these the diagnosis has not been proved either roentgenographically or at operation. These cases are presented in brief in the accompanying table. It will be noted that in several cases a slight icteric tint was reported, but unless a definite diagnosis of jaundice was made this condition was incorporated in the table as questionable. The results of cholecystographic study are available, naturally, only in cases observed since 1924, when the method was first introduced by Graham and Cole.

Only 1 of the 9 patients in whose cases the information was given was left handed. Ten were females, and 7 were males, the sex of 1 was not mentioned. In 11 of the 16 cases in which the location of pain and tenderness was mentioned, the left upper quadrant of the abdomen and the back were the major points of involvement. In 2 instances most of the discomfort was on the right side, and in 3 it was in the epigastrium. These figures show that the tendency of pain to be referred to the right from a viscus transposed to the left is not so great with cholecystitis as with appendicitis. As has been stated, in more than one half of the cases of appendicitis associated with situs inversus there are localizing signs indicative of disease in the right lower quadrant of the abdomen. Our patient is one of only 2 with disease of the gallbladder and situs inversus in whom most of the discomfort was in the right upper quadrant. These facts make the anatomic and pathologic diagnosis of "left-sided" cholecystitis somewhat easier than that of "left-sided" appendicitis. Furthermore, one is usually warranted in allowing a longer period for observation and study of patients in whose cases cholecystitis is suspected than of those for whom acute appendicitis is feared.

There is no evidence to indicate that disease of the biliary tract is more common in persons with situs inversus than in the general popu-

Author	Patient	Duration and Nature of Symptoms
Billings, F Two Interesting Cases Philadelphia M J G 670, 1900	White woman aged 39 sextipara, left handed White man aged 64 right handed	14 years of head aches and colicky pain in left lumbar region 5 years of intermittent pain indigestion chill fever and jaundice Mentioned case but gave no history
*Mayo, W J, in Keen W W Surgery Its Principles and Practice, Philadelphia, W B Saunders Company, 1914 vol 3, p 969 Kehr H Liebold, and Neuling Drei Jahren Ballenstein Chirurgie Bericht uber 312 Laparotomien am Gallensystem aus den Jahren 1904 1906, Munich, J F Lehmann, 1908, p 329	Man aged 55	13 years of intermittent colicky pain in left upper quadrant of abdomen
Hupp, F L Malpositions of the Liver New York M J 94 423 1911	Woman, bipara, 3 times pregnant right handed	4 years of intermittent pain jaundice and loss of weight
Horn, H W Situs Viscerum Inversus with Gallstones, Ann Surg 62 424, 1915	White woman aged 51, quadripara	30 years of dull aching pain indigestion and eructation
Kelly R E Transposition Associated with Gallstones and Hourglass Stomach Brit J Surg S 137, 1920	Woman aged 40 bipara right handed	3 years of colicky pains related to ingestion of food and relieved by vomiting
Bell G and Winn R C Cholecystitis in a Patient with Transposition of Viscera M J Australia 1 339, 1920	Man aged 57 right handed right testicle lower	24 hours of severe pain
Frischmann E S Cholelithiasis with Situs Inversus, Brit M J 2 811, 1923	Woman aged 43 tripara right handed	3 months of late intermittent pain with jaundice
Bettman R B, and Binswanger, H F Cholecystitis Associated with Situs Transversus Am J M Sc 172 570 1926	Man aged 49 right handed	Few hours of excruciating pain with a history of 2 similar attacks in past
Galindez A and Delrio, J M Sindrome coledociano y periduodenitis en una transposición total de visceras Bol y trab de la Soc de cir de Buenos Aires 14 1011, 1930	Man aged 25 right handed left testicle lower	Since childhood epigastric pain relieved by food few months of attacks of pain in left upper abdominal quadrant and jaundice
Counseller V S Rupture of Spleen Gunshot Wounds of Abdomen, Transposition of Organs Report of Cases Proc Staff Meet, Mayo Clinic, 6 504, 1931	Man aged 23	2 years of late intermittent pain a frequent eructation acute pain shortly before admission
Carnot, P Coliques hépatiques a gauche dans un case d'inversion viscérale, Paris méd 2 537, 1931	Woman aged 32 bipara	3 months of late intermittent colicky pain in left upper abdominal quadrant
Beltrametti, L Sopra un caso di colecistite probabilmente calcicola in soggetto con situs viscerum inversus totalis, Giorn de clin med 14 93, 1933	Girl aged 17	6 months of late intermittent pain occasionally associated with vomiting and fever not stated
Troutt J M Situs Transversus Viscerum—Case with Cholelithiasis, Ann Surg 98 1169 1933	Woman aged 45	
Tirczak C Cholecystektomie bei Situs inversus totalis, Zentralbl f Chir 61 1172, 1934	Woman aged 40	6 years of late intermittent colicky pain with indigestion and loss of weight
Baru R J, and Isasi E Inversion total de visceras litiasis biliar y pequeño quiste hidático intrahepático, Arch urug de med, cir y especialid 9 191, 1936	Man aged 24	Obstinate constipation for 3 years intermittent indigestion and eructation 5 months

* In a recent communication Balfour⁹ stated that the operation mentioned was performed for an intestinal obstruction secondary to a retroperitoneal dermoid and that the findings in the gallbladder were normal

Pain		Findings	Complications	Preoperative Diagnosis of Transposition	Roentgen Confirmation		Operation	Results
Location	Radiation				Transposition	Disease of Gallbladder		
Left lumbar region	No	Palpable left kidney and resistance at left costal margin	Dilatation of left kidney	Yes	Yes	No calculi noted	Nephropexy (left) and subsequently cholecystostomy with removal of 4 stones	Uneventful recovery
Epigastrium	No	Hard mass at left costal margin	Obstructive jaundice	Yes	No	No	Cholecystostomy with removal of one large stone from cystic duct	Death 4 days after operation
Left upper abdominal quadrant	No	No tenderness	Chronic productive cough obstructive jaundice	Yes	Yes	No calculi noted	Stone removed from common duct drainage of common duct	Uneventful recovery
Epigastrium	To left	Tenderness over entire epigastrium	4½ months pregnancy obstructive jaundice	No	No	No	Cholecystostomy with removal of 2 stones from the cystic duct	Uneventful recovery and subsequent normal delivery
Left upper abdominal quadrant	To left scapula	Tenderness in left upper quadrant of abdomen		Yes	Yes	No calculi noted	Cholecystostomy with removal of 4 stones	Uneventful recovery
Epigastrium and right upper abdominal quadrant	To right scapula		Hourglass stomach from ulcers on lesser curvature	Yes	Yes	No calculi noted	Posterior gastroenterostomy and cholecystectomy gallbladder full of stones	Uneventful recovery
Left upper quadrant of abdomen	No	Marked tenderness and rigidity of left upper quadrant of abdomen	Syphilis of 12 years' duration	Yes	Yes	No calculi noted	Cholecystostomy gall bladder was acutely inflamed and contained one large stone	Secondary cholecystostomy performed on 37th postoperative day with recovery
Left upper quadrant of abdomen	To back and left shoulder	Indefinite tender mass in left upper quadrant of abdomen	Obstructive jaundice	Yes	Yes	No calculi noted	Cholecystectomy and choledochotomy with removal of stones from both gallbladder and common duct	Subsequent course uneventful
Left upper quadrant of abdomen	To left scapula	Tenderness and rigidity in left upper quadrant of abdomen	Jaundice ?	Yes	Yes	Shadow of gallbladder seen on left no calculi noted	Refused	Improvement after 3 days hospitalization
Epigastrium and left upper quadrant of abdomen	No	Tenderness in left upper abdominal quadrant with tender palpable liver on left	Jaundice ?	Yes	Yes	No calculi noted cholecystogram not mentioned	Cholecystectomy and appendectomy gall bladder contained no stones	Uneventful recovery
Epigastrium	Not mentioned	Rigidity in left upper quadrant of abdomen		Yes	Yes	Cholecystogram gallbladder nonfunctioning	Cholecystectomy and appendectomy gall bladder contained many stones	Uneventful recovery
Left upper quadrant of abdomen	To left scapula and shoulder	Tenderness at left costal margin	Jaundice ? ("subicterus")	Yes	Yes	Cholecystogram showed gall bladder on left no stones	None medical regimen instituted	Not stated
Epigastrium and left upper quadrant of abdomen	To left scapula on 1 occasion	Tenderness in left flank with palpable liver on the left		Yes	Yes	Cholecystogram, gallbladder did not visualize no stones	Refused	Not stated
Not stated	Not stated	Not stated	(1) Chronic arthritis (2) chronic pyelitis	Yes	Yes	Multiple faceted stones	Cholecystectomy and appendectomy	Uneventful recovery
Left upper quadrant of abdomen	Not stated	Fist sized mass in left upper quadrant of abdomen		Yes	Yes	Calculi not noted	Cholecystectomy gall bladder contained stones	Uneventful recovery
Left upper quadrant of abdomen	To left side of back	Generalized tenderness and spasticity	Intrahepatic hydatid cyst jaundice ?	Yes	Yes	Cholecystogram gallbladder did not fill intrahepatic cyst seen	Not stated	Not stated

lation Although situs inversus is usually perfectly compatible with normal health and longevity, there is some evidence that persons with this condition have a higher percentage of congenital abnormalities The findings of Kartagener²⁰ and those of Adams and Churchill⁸ show conclusively that the incidence of bronchiectasis in persons with situs inversus is markedly increased The latter authors stated "The incidence of bronchiectasis in the 23 cases (Massachusetts General Hospital) of situs inversus is 21.7 per cent The incidence of bronchiectasis in the hospital population is 0.036 per cent The incidence of situs inversus in the hospital population is 0.002 per cent" One of the 5 patients with situs inversus observed in the Vanderbilt Hospital in the past twelve years had bronchiectasis

SUMMARY

Seventeen cases of situs inversus and disease of the gallbladder have been found in the literature, and an additional case is reported The pain of appendicitis in a person with transposition of the viscera is usually on the right side, the pain of disease of the gallbladder is usually on the left As a result of studies on appendicitis, cholecystitis, bronchiectasis and other diseases, the status of situs inversus has changed from that of an anatomic curiosity to that of a clinically important entity Its early recognition is very important in some surgical emergencies

²⁰ Kartagener, M Zur Pathogenese der Bronchiektasien, Beitr z Klin d Tuberk **83** 489, 1933, **84** 73, 1933, **87** 331, 1935

SURGICAL TREATMENT OF SIGMOIDOVESICAL FISTULAS

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The creation of a sigmoidovesical fistula by a process primary in either the sigmoid flexure of the colon or the urinary bladder is a serious complication which fortunately confronts the surgeon only infrequently. It engenders so poor a prognosis that the choice of treatment must be guided by great care, for the mortality resulting from surgical attack is extremely high. The pathologic entity responsible for the formation of such an abnormal channel is usually primary in the sigmoid and but rarely has its origin in the bladder. Occasionally an inflammatory process external to both sites may be the responsible agent. Parham and Hume,¹ Sutton² and Kellogg³ have each presented excellent classifications of the causes of sigmoidovesical fistula.

The frequency of communication between the sigmoid flexure of the colon and the urinary bladder as compared to other intestinovescical fistulas has gradually increased since the earlier reports. Pascal⁴ found involvement of the sigmoid flexure in 18 per cent, Albano⁵ in 45 per cent, Sutton in 57 per cent and Kellogg in 63 per cent of their respective series. In a review of 385 cases, Parham and Hume reported that in only 33 cases (11 per cent) were sigmoidovesical fistulas observed in the 278 patients with enterovesical fistula for whom the location of the lesion was stated. Higgins⁶ has reported that the sigmoid flexure and the urinary bladder were involved 95 times in a total of 406 cases of vesicointestinal fistula.

From the Division of Surgery, the Mayo Clinic

1 Parham, F W, and Hume, J Vesico-Intestinal Fistulae, *Ann Surg* **50** 251-286 (July) 1909

2 Sutton, C D Vesicosigmoidal Fistulae, *Surg, Gynec & Obst* **32** 318-327 (April) 1921

3 Kellogg, W A Vesico-Intestinal Fistula, *Am J Surg* **41** 135-186 (July) 1938

4 Pascal, cited by Kellogg³

5 Albano, G Contributo clinico allo studio delle fistole vescico-intestinali, *Arch ital di chir* **16** 133-172, 1926

6 Higgins, C C Vesico-Intestinal Fistula, *J Urol* **36** 694-709 (Dec) 1936

Although slight variations due to the causative factor may be present, the general syndrome presented by patients with sigmoidovesical fistula is essentially constant. As a rule, those with diverticulitis state that the condition was gradual in onset. Repeated attacks of pain in the left lower abdominal quadrant, abdominal cramps and left iliac tenderness occur because of the diverticulitis. Simultaneously with the last-mentioned symptom, or perhaps later in the course of events, burning and frequency of urination occur. Micturition may occur hourly and may be accompanied by a scalding pain either during or at the completion of the act. Chills and elevations of temperature complete the syndrome of sigmoidovesical fistula.

With the establishment of fistula into the bladder, bubbles of gas may be passed through the urethra, usually at the end of micturition, but the passage of feces does not occur as frequently as does that of flatus. The fecal content of the urine is conditioned by the state of the bowels, for when they are in a constipated state little or no feces will be seen. However, the onset of fluid stools increases the quantity of fecal material in the urine. In some patients the start of all their difficulty is marked by a gush of air and feces through the urethra. When the ordinary flow in such a fistula is reversed and the urine is diverted into the bowel, slight laxity of the bowels or chronic diarrhea may result.

Symptoms referable to the urinary bladder alone were present in 8 patients with fistula. Only after careful examination was the true etiologic factor in the colon discovered. Six patients with diverticulitis of the sigmoid flexure and 2 with a malignant lesion in the same locality complained only of symptoms associated with cystitis. Conversely, an occasional patient, like 1 of those with a malignant lesion in the present series, may give no subjective information and have no objective signs when a fistula is present, except a little pus or blood in the urine. The communication is discovered only when exploratory laparotomy is performed.

From the diagnostic standpoint, a history of passage of gas and feces through the urethra is pathognomonic. Instances have been reported in which an unsuspected opening into the bladder was found on cystoscopic examination, but this occurs infrequently, and usually a definite history of difficulty with the bladder is obtained. The quantity of pus in the urine varies, and occasionally erythrocytes in small number are seen on microscopic examination of the urine. Gross hematuria is noted less frequently.

Cystoscopic examination, of course, is necessary and invaluable in the diagnosis. A fistulous opening, usually on the left side of the bladder, may be visualized, but frequently this is not seen, for a mass of granulation tissue or a depressed necrotic region in the bladder may be the

only evidence there that a fistula exists. By means of the cystoscope gas may be seen to bubble through the opening and occasionally feces may exude. When a suspicion exists that a fistulous tract is present, a lead catheter may be passed gently through the necrotic region and a roentgenogram taken. The shadow cast by the catheter may then be seen in the colon. Force should not be used, as the possibility of creating a false passage is a definite menace. Cystograms may aid the diagnostician in that the mediums may outline the tract.

Methylene blue may be injected into either the bladder or the rectum and its passage from the corresponding location awaited. When a positive result is noted, conclusive proof of fistula is present.

Proctoscopic procedures, although a valuable aid in some cases, are not usually of much help in visualization of the intestinal opening of the tract. In most cases the aperture is too high to be seen, also, the inflammatory changes in the bowel may obscure the primary opening. However by direct observation and perhaps a biopsy of material from the lesion, the proctoscopist many times can make a decision as to the etiologic agent.

Likewise, by indirect observation, the roentgenologist may state the correct nature of the lesion. He may also see the tract, outlined by barium sulfate, leading from the sigmoid flexure to the urinary bladder.

Pneumaturia, although helpful in the diagnosis of fistula, is not pathognomonic. The etiology of pneumaturia has been fully discussed by Kelly and MacCallum,⁷ Hinman⁸ and Riley and Bragdon.⁹ Introduction of air into the bladder during catheterization or therapeutic procedures will result in its passage later, and this should be clearly distinguished from true pneumaturia. Gas entering the bladder from the intestinal tract is a second etiologic agent. Also to be demarcated from the group of patients with vesicointestinal fistula are those diabetic patients in whom the passage of gas through the urethra is the result of decomposition or fermentation of urine in the bladder by yeast organisms. In occasional cases of chronic infections of the renal pelvis or of the bladder pneumaturia may occur. The offending bacterial organisms include *Escherichia coli*, *Aerobacter aerogenes* and *Coccobacillus vesicae*.

Complicating the formation of a fistula are a number of secondary infections of the genitourinary system. Symptoms referable to cystitis are greatly increased at the time the fistula becomes complete. Pyelitis and pyelonephritis are of infrequent occurrence in spite of the number

⁷ Kelly, H. A., and MacCallum, W. G. Pneumaturia, *J. A. M. A.* **31** 375-381 (Aug. 20) 1898.

⁸ Hinman, F. *The Principles and Practice of Urology*, Philadelphia, W. B. Saunders Company, 1935.

⁹ Riley, F. G., and Bragdon, F. H. Pneumaturia in Diabetes Mellitus. Report of a Case, *J. A. M. A.* **108** 1596-1599 (May 8) 1937.

of cases of necrotic cystitis observed. Likewise, the formation of stones in the bladder is rare. Of great importance is the psychologic effect on the patients of the passage of discharges through unnatural channels. This is true particularly of those patients who are reduced to a diaper era by rectal incontinence of urine. They become mentally depressed and despondent.

In 1921 Sutton reported from this clinic the cases of 34 patients with sigmoidovesical fistula. In this group there were 3 in whom the condition was due to trauma, 23 in whom it was due to inflammatory conditions exclusive of diverticulitis, 6 in whom it was due to diverticulitis and 2 in whom it was caused by carcinoma. If the present series is combined with that of Sutton, a total of 88 patients have been observed (table 1).

Certain comparisons between the two groups of patients are of interest. Sutton reported observing fistulas in 26 women and 8 men, while in the present series there were 9 women in contrast to 45 men.

TABLE 1—*Etiologic Factors in Eighty-Eight Cases of Surgically Treated Sigmoidovesical Fistula*

Traumatic factors	3
Inflammatory factors	33
Diverticulitis	36
Carcinoma	14

This difference is accounted for by the fact that salpingitis, specific or nonspecific, was the etiologic factor in a majority of Sutton's series, while it was not encountered in the present series. However, fistulas due to diverticulitis have increased from 6 in Sutton's series to 32 in the present. A somewhat smaller increase has also been seen in the number of fistulas resulting from carcinoma.

Diverticulitis is perhaps the leading cause of sigmoidovesical fistula. Diverticula of the colon occur most frequently in the sigmoid flexure, and, according to Rankin and Brown,¹⁰ a trifle more than 5 per cent of patients at the Mayo Clinic on whom roentgen studies of the colon were made were found to have diverticula. Rankin and Brown's statistics further reveal an incidence of diverticulitis in about 17 per cent of patients who had diverticula.

The pathologic sequence of events culminating in sigmoidovesical fistula due to diverticulitis may be reconstructed in the following manner. Once a diverticulum is formed, it tends to undergo progressive enlargement. With such progression, the muscular coat of the colon gradually disappears, and, since a small sac with a narrow neck is

10 Rankin, F. W., and Brown, P. W. Diverticulitis of the Colon, *Surg Gynec & Obst* 50: 836-847 (May) 1930.

present, the fecal contents are retained. Mechanical irritation amidst great numbers of micro-organisms results in an inflammatory process, which involves the peridiverticular tissues as well as the diverticulum itself. Marked extension of this process results in timefaction and stenosis of the lumen of the bowel with perforation and localized abscess formation as further complications of the original condition. Such abscesses usually do not perforate into the general peritoneal cavity but are well walled off by dense adhesions. Mesosigmoiditis causing the mesentery to be extremely friable is a further complication, which is sometimes not appreciated until surgical attack on the bowel is made. In a small number of patients with perforating diverticulitis the inflamed and perhaps redundant loop of sigmoid flexure will drop low into the pelvis and become either directly or indirectly attached to the bladder. Symptoms of cystitis may be present before actual perforation with establishment of a fistula occurs. The creation of an abnormal channel may or may not be preceded by the formation of an abscess cavity between the sigmoid flexure and the bladder.

Probably the earliest authentic description of a patient with diverticulitis complicated by a sigmoidovesical fistula was reported by Friend.¹¹ He wrote that his male patient was "seized with a pain, flatulency and a sort of convulsion in his bowels." The patient then passed "pus and gas per urethram for three months." Necropsy showed an inflamed mass of the colon with a hole into the bladder "the size of a goose quill." Another of the earlier reports of a vesicointestinal fistula which may have been due to diverticulitis is referred to by Morgagni.¹² The reference is given in one of his engagingly communicative letters, the whole of which form one of the fundamental works of modern pathologic anatomy. Discussing an ulceration of the urinary bladder, Morgagni continued

and, as in one, the whole bladder is said to have been ulcerated, you will also partly suspect, that an ulcer had reached from thence into some one, or other, of the intestines.

For it might easily happen, that a bladder, in this state, should coalesce with one of the nearest intestines, and that thus a winding sinus might be formed, by means of a kind of ulcerous corrosion, from the one to the other. And in this manner, we may perhaps conceive how the man of whom Young writes, discharg'd, together with a foeculent urine, very small grapes, and particles of leaves, and roots and other things which he had eaten, and with these two pills drawn out into a considerable length

¹¹ Friend, cited by Wetherell, F. S. The Diagnosis and Management of Diverticulosis and Diverticulitis of the Pelvic Colon in Women, *Am J Obst & Gynec* 35 417-425 (March) 1938

¹² Morgagni, G. B. The Seats and Causes of Diseases Investigated by Anatomy, in Five Books Containing a Great Variety of Dissections, with Remarks, to Which Are Added Very Accurate and Copious Indexes of the Principal Things and Names Therein Contained, translated from the Latin by B. Alexander, London, Millar & T. Cadell, 1769, vol 2, p 541

It is certain that very severe colic pains had preceded in the former months, so as to make it not altogether improbable, that some inflam'd intestine had coalesc'd with the bladder, and a small abscess being made, that pus had been discharg'd into the cavity of both these viscera, by which a fistula of communication might have been left open betwixt them

For as to the urine having no disagreeable smell, when Young was call'd to the patient, and as to neither blood, nor pus, being discharg'd in the stools, as to there being no tenesmus, and as to the unctuous fluid, given in the form of a glyster, not having ting'd the urine with its colour, it is true that these circumstances might, with good reason, render it less supposable, with him, that there was a communication betwixt the bladder and the rectum, or betwixt the bladder and the colon

Another excellent authentic description of a fistula due to diverticulitis with a report of the postmortem examination was that of Jones¹³ A 64 year old woman had passed gas and feces through the urethra The situation was further complicated by a calculus in the urinary bladder At postmortem examination about 3 inches (7.6 cm) of the sigmoid flexure was found to be somewhat contracted A large number of diverticula were present Ulceration had occurred at the base of one, allowing the formation of an abscess external to the bowel The abscess in turn had communicated with the urinary bladder

In the review of enterovesical fistula by Parham and Hume, the fistula was definitely stated to have been caused by diverticulitis in only 3 cases, while in 65 the cause was classified as inflammatory No doubt in many cases of the latter group the fistula was caused by diverticulitis Bryan¹⁴ reported a series of 43 fistulas, and of these 17 were certainly, and 2 were probably, due to this condition In 18 per cent of Sutton's cases diverticulitis with perforation was the etiologic agent

Gouverneur, Soupault and Latifi¹⁵ found 38 fistulas (11 per cent) in 324 cases of diverticulitis of the sigmoid Higgins collected 328 cases of vesicointestinal fistula and reported that in 160 the fistula was the result of an inflammatory condition Ninety-two cases of diverticulitis were included in the series There were 12 cases of fistula in a recent series of 91 cases of diverticulitis in which operation was done by Lockhart-Mummery¹⁶ Of the 54 sigmoidovesical fistulas described in this presentation, 32, or 59 per cent, were caused by the same pathologic entity

13 Jones, S Communication Between the Sigmoid Flexure and the Bladder, the Result or Ulceration of a False Diverticulum, *Tr Path Soc London* 10 131 132, 1859

14 Bryan, R C Sigmoidovesical Fistula, with Report of a Case, *Ann Surg* 63 353-363 (Feb) 1916

15 Gouverneur, R, Soupault, R, and Latifi, M Les fistules colo vésicales d'origine diverticulaire, *J de chir* 51 215-231 (Feb) 1938

16 Lockhart-Mummery, J P Late Results in Diverticulitis, *Lancet* 2 1401 1404 (Dec 17) 1938

Most of the patients with diverticulitis complicated by fistula were men (97 per cent), and the average age was 54.8 years. Men are affected in greater numbers because diverticulitis is more frequent in that sex and an additional fact is that in women the uterus forms an effective barrier between the sigmoid flexure and the bladder. Symptoms referable to disturbance in the urinary bladder were present for periods varying from a few days to many years. There was passage of either gas or feces through the urethra in practically all the cases.

Varying degrees of cystitis were seen through the cystoscope, and visualization of the fistulous opening was possible in 13 of the 30 patients examined cystoscopically. In 9 the aperture was on the left, in 1 it was on the right and in 3 it was in the dome of the bladder. Demonstration of the fistulous tract was possible in only 1 of the 10 cystograms made. Owing to its proximal position, the colonic opening of the fistula to the bladder was seen through the proctoscope in only 1 of the 29 patients subjected to examination. Although the roentgenogram was valuable in demonstrating the regional extent of diverticulitis, the fistulous tract was demonstrable on only one occasion.

The problem of curative treatment of vesicointestinal fistulas in general has brought forth a number of surgical procedures. Barbier de Melle¹⁷ proposed the first rational treatment by suggesting colotomy. Pennel,¹⁸ Curling¹⁹ and Holmes²⁰ were among the pioneers to employ this operation. Suprapubic cystostomy followed by intravesical closure of the vesical opening was suggested in 1884 by Le Dentu.²¹ This method was used by Pousson²² eleven years later, with temporary success but ultimate failure. Czerny²³ and Boiffin²⁴ were the earliest champions of an intraperitoneal approach to surgical correction of the fistula.

A true evaluation of the surgical methods used in the treatment of sigmoidovesical fistula due to diverticulitis is difficult to attain, since

17 Barbier de Melle, cited by Chavannaz, G. Des fistules vesico-intestinales acquises chez l'homme, *Ann d mal d org genito-urin* **15** 1176-1199, 1897, **16** 203-217, 1898.

18 Pennel, C. A Case of Stricture of the Rectum, Wherein an Artificial Anus Was Established in the Left Lumbar Region, with Remarks, *Lancet* **1** 628, 1850.

19 Curling, cited by Parham and Hume.¹

20 Holmes, T. A Case of Lumbar Colotomy (Amussat's Operation) Successfully Performed for the Relief of Vesico-Intestinal Fistula, *Lancet* **1** 400-401 (April 14) 1866.

21 Le Dentu, cited by Parham and Hume.¹

22 Pousson, cited by Parham and Hume.¹

23 Czerny, cited by Parham and Hume.¹

24 Boiffin. Retrecissement du colon ascendant, abces couvert dans le rectum et la vessie. Enteroanastomose, *Bull et mem Soc d chir de Paris* **17** 305-309 (April) 1891.

the majority of case reports are deficient as to details of the procedure used. In addition, the actual number of patients with diverticulitis suffering this unfortunate complication is small. A large series must be accumulated before adequate judgment as to the true value of any single procedure can be formed. With a small group, if end results are expressed on a percentage basis a false conception as to efficacy of treatment and mortality may be entertained. If only 3 patients in the whole series are subjected to one procedure and 1 succumbs, the mortality thus stated would be 33.3 per cent. However, the same operation employed on 3 other patients might result in three cures. Therefore, the expression of results by the percentage system will be avoided here, and only actual statistics will be presented.

A survey of the existing literature yields a number of methods used in the surgical attack on fistula due to diverticulitis. The three chief avenues of approach are (1) colostomy or cecostomy alone, (2) a single stage procedure with or without the establishment of an artificial abdominal anus and (3) a multiple stage operation. Diversion of the fecal current and subsequent surgical treatment of the fistulous tract and adjoining regions by varied methods are the main components of the multiple stage operation. Included among such methods are (1) excision of the tract with simple closure of the sigmoidal and vesical openings, (2) closure of the aperture in the bladder combined with a Paul-Mikulicz procedure on the involved portion of the sigmoid flexure and (3) suture of the vesical opening and resection, with end to end anastomosis of the diseased sigmoid flexure. Surgical mortality attendant on such procedures as a whole is markedly elevated but varies considerably between individual approaches.

Simple colostomy as close as is practicable to the site of the lesion is the simplest way of handling the problem, and, as would be expected, the primary mortality rate from such a procedure is low. At this point, it is well to keep in mind that when colostomy is performed it should be designed with the purpose of preventing spilling from the upper barrel into the lower barrel. If sufficient time is allowed to elapse, often the fistula will close spontaneously if the fecal current has been well diverted. If the colonic stoma is not placed as close as is feasible to the inflammatory mass, a large amount of inspissated material may collect in a redundant loop of bowel between the colonic stoma and the region of inflammation. This should be avoided if possible. Cecostomy should be employed, perhaps, only if marked obstruction is present and then as a preliminary to colostomy.

Two patients of the present group have been reported on previously, and their cases have been reviewed by Kellogg. When these are deducted from his series, there are left 28 cases of fistula due to diverticulitis and 7 of fistula probably due to it. Thirteen patients in all were sub

jected to colostomy and 11 were cured. One remained unimproved, and 1 died. This last figure is of great importance.

One stage procedures were performed in 12 cases of Kellogg's series. These included (1) primary separation and suture of the bladder and intestine, (2) primary separation, repair of the bladder, resection of the bowel and end to end anastomosis, (3) the first procedure described, with the addition of a permanent colostomy, (4) the same procedure, except that a cecal stoma was established instead of a vent in the more distal portion of the colon, (5) primary separation of the bowel, repair of the bladder, resection of the bowel with end to end anastomosis and cecostomy, and (6) primary separation repair of the bladder, resection of the sigmoid flexure (method not stated) and permanent colostomy. With the first procedure, 2 patients were cured and 1 died, with the second, 2 were cured, with the third, 1 was cured, with the fourth, 2 died, with the fifth, 1 was cured, and with the sixth, 2 were cured and 1 died.

Four patients were subjected to a multiple stage operation. An artificial abdominal anus was made in some portion of the colon proximal to the lesion and at a subsequent date separation and suture of the sigmoid flexure and urinary bladder were done. The abdominal vent was made permanent in only 1 case. All of these patients were cured.

Of the 17 patients in this group on whom colostomy was performed either as a total therapeutic procedure or as a preliminary to secondary operations, only 1 died. The results were good also in the group treated with resection secondary to colostomy, in which there were no deaths attributable to the latter procedure.

To arrive at a more complete evaluation of the surgical procedures used in the present series of fistula due to diverticulitis, 6 cases previously reported by Sutton are added. Multiple modes of treatment were used in these 38 cases, inasmuch as the procedures were performed by a number of different surgeons over a period of thirty-two years.

On 8 patients of this group colostomy alone was performed, without primary operative mortality. Likewise, there were no deaths in an additional group of 11 patients in whom an abdominal fecal vent was made preparatory to subsequent operations. One of the patients in the latter group was operated on elsewhere.

A primary attack on the fistula itself, varying in detail, was used in 16 cases. In the largest proportion (8 cases) there were performed primary separation of the involved parts and suture of the bladder and intestine. There was 1 recurrence, one year after the operation. Three postoperative deaths from peritonitis resulted. Transverse colostomy was performed in an additional case in which there had been the same primary attack on the fistula. Closure of the aperture in the bladder and exteriorization of the affected bowel as a Paul-Mikulicz operation

was performed in 5 cases, with 2 "primary" deaths. The vesical opening was sutured and resection with end to end anastomosis over a rubber tube was done in another case, with a favorable result. The last-mentioned type of procedure with the addition of appendectomy was performed in an additional case, with resulting cure. In the group as a whole there were 5 deaths directly attributable to the surgical procedure.

Diversion of the fecal stream from its natural channel and a secondary approach to the fistula were made in 12 cases. Second stage procedures were performed at periods varying from about three weeks to five years and five months. Resection of the involved portion of bowel by the Paul-Mikulicz operation was employed in 4 instances, resection with end to end anastomosis in 5 instances and separation and simple closure of the openings in 2. In 1 case anterior resection was performed, but the distal end of the bowel was closed and dropped back into the pelvis. Two of the patients subjected to each of the first two procedures and the 1 subjected to the last procedure died. However, of the 5 deaths, 3 were but indirectly due to the surgical procedure. Evisceration followed by peritonitis was responsible for the death of 1 of the patients whose sigmoid flexure had been exteriorized, a hemorrhage on the twenty-fifth postoperative day accounted for the death of another patient, in whom a primary anastomosis had been made, and a third died of a fatal pulmonary embolus.

The length of the interval between operations depends on the general condition of the patient and the reaction of the fistula to the passage of time. Certainly the interval should be at least six months to one year to allow spontaneous closure of the fistula. In this particular study the lapse of a longer period seemed to have no effect on mortality.

In 2 other patients in this group with diverticulitis primary separation of the involved viscera and repair of the openings were performed. However, a recurrence of symptoms in both necessitated further surgical procedures. In 1 the vesical opening was again closed and the involved portion of the sigmoid flexure exteriorized, with resulting cure. Intra-vesical closure of the fistulous tract and establishment of a colonic stoma above the site of the lesion resulted in improvement in the other patient. However, he succumbed to an unrelated illness while at the clinic, so that a true evaluation of the end result could not be obtained.

Computation of results reveals cures in 15 cases and 10 "primary postoperative" deaths. Two additional patients secured excellent results from operation but unfortunately had a persistent fecal fistula at the site of colostomy. Recurrences took place in 2 patients seven and nine years respectively after operation. One patient had undergone primary separation of the sigmoid flexure and the bladder with closure of the

openings on the second a colostomy had been performed, with later closure of the openings as has been described. The colonic stoma was subsequently closed.

Several interesting facts are presented in connection with the group of patients on whom colostomy was performed as the sole surgical procedure. Three patients had no relief from the operation, but further surgical intervention was prohibited in 1 by age and poor general condition. When last seen, 1 patient had improved to such an extent that he was to return for a resection of the sigmoid flexure. Two other patients obtained excellent results from colostomy, but when the abdominal colonic stomas were closed recurrence of symptoms referable to the fistula took place. The closure in 1 of these patients broke down, and a fecal fistula resulted. Colostomy was again performed elsewhere in the other patient in whom recurrence was noted, and he subsequently succumbed to an operation of unknown character, presumably on the sigmoid flexure. Death from an unrelated cause claimed an additional patient in this group. The reason for the death of the last patient could not be ascertained.

The procedure of choice for any given patient cannot, of course, be postulated. Any number of conditioning factors must affect the surgeon's choice. Age, general physical status, amount and degree of involvement of the affected bowel, the exact location of the inflamed region and the condition of the mesentery are but a few of the necessary factors demanding evaluation before decision as to a definite operation is made. A friable mesentery and bowel will make suturing difficult, as the sutures will pull out easily. Infection will be spread more easily, notwithstanding meticulous technic. When the region of diverticulitis is proximal in the sigmoid flexure, exteriorization may be carried out, resection with end to end anastomosis may be necessary in the more distal portion. A slight amount of inflammation may permit primary separation of the adherent structures and suture of the openings.

However, the lessons learned in surgical treatment of the bowel for other conditions are readily applicable to diverticulitis with fistula, for the same general principles hold. It would seem, therefore, that any conservative approach to cure should include a preliminary colostomy close to the site of the lesion. Furthermore, such a vent should be absolute, so that fecal material will not go over the spur and eventually reach the diseased bowel. If the symptoms subside and the fistula closes spontaneously, the colonic stoma may be subsequently closed. This operation, however, should be performed only if a sufficient interval has elapsed to allow complete subsidence of the inflammatory process in the sigmoid flexure. This must be checked by proctoscopic and roentgen studies in addition to thorough consideration of the patient's course after colostomy had been performed. Occasionally, however, one

observes a favorable result from colostomy, with subsidence of the diverticulitis and closure of the fistula, but when the abdominal colonic stoma is closed, symptoms referable to the sigmoidovesical fistula are again present. In such a case, resection of the involved portion of bowel after preliminary colostomy will have to be done if cure is to be effected.

If resection of the sigmoid is decided on after a sufficient interval, the type of operation used should depend to some extent on the exact location of the lesion in the sigmoid flexure. Whenever possible, a Paul-Mikulicz operation is the procedure of choice for the upper part of the sigmoid flexure. Occasionally a lesion distal in the bowel may be exteriorized by opening the pelvic peritoneum and freeing the colon. If this is not possible, resection and end to end anastomosis may be necessary.

Free drainage of the urinary bladder is essential and may be achieved by either a suprapubic tube or an indwelling urethral catheter. The latter also offers a means of irrigating the bladder.

It may be well at this point to quote from no less eminent an authority than Harrison Cripps,²⁵ who wrote in 1888: "The idea of abdominal section with a view to separating the intestine from the adherent bladder and closing the openings might at first be thought possible, but after investigating museum specimens and the accounts of postmortem examinations, the proceeding, I fear, will be seldom practicable."

Carcinoma of the sigmoid flexure was responsible for the fistula in 12 patients. Differentiation of a malignant lesion from a region of diverticulitis may be extremely difficult at times. The average age of these patients was 49.7 years, and all except 2 were men. The symptoms in general were similar to those encountered in the group with diverticulitis. Proctoscopic examination, roentgen studies of the colon and cystoscopic examination were useful adjuncts in establishing the diagnosis.

Particular attention should be called to 2 patients who presented on primary cystoscopic investigation large tumor masses in the bladder. If the entire situation is not carefully reviewed, an error in diagnosis may be made. Vesicosigmoidal fistula due to primary carcinoma in the urinary bladder is extremely rare, and the lower part of the colon should be thoroughly investigated in all cases in which the fistula is thought to be due to a neoplasm of the bladder.

Invasion of the wall of the bladder by a malignant growth of the sigmoid flexure engenders an extremely poor prognosis. However, if metastases are not demonstrable operation should be undertaken. The type of operation depends on the particular skill of the surgeon and the exact situation of the growth. In any event, the involved portion

²⁵ Cripps, H. Passage of Gas and Feces Through the Urethra. Colotomy, Recovery, Remarks, *Lancet* 2:619-620 (Sept. 29) 1888.

of the bladder must be resected and the bladder closed. Suprapubic cystostomy may be performed or the bladder drained with an indwelling catheter. Of the 12 patients, 11 succumbed either immediately after the operation or shortly thereafter. The fate of the other patient in this group is unknown but he had an inoperable lesion at the time of operation, so that a palliative colostomy was performed.

In the group with sigmoidovesical fistula there were 9 patients whose fistula was due to an inflammatory condition which was not diverticulitis and 1 with an inflammatory condition which might have been diverticulitis. Six of these patients were women, and 4 were men. The average age of the entire group was 42.8 years. Six were simply classified as having an inflammatory condition, 1 as having an inflammatory condition and a questionable malignant lesion and 2 as having tuberculosis. Seven of the patients in this group had undergone an abdominal operation elsewhere previously, the fistula being the result of infection following operation. One of the patients had had a tuberculous ovary removed here, and a sigmoidovesical fistula had developed postoperatively. The symptoms referable to the fistula were the same for the whole group as have been described previously.

As would be expected surgical approach to the group of inflammatory lesions was most difficult. The intestines are usually adherent to one another and the surrounding structures, making any procedure hazardous. In addition, the patients usually have been ill for prolonged periods and have lost considerable weight and strength. Primary separation of the sigmoid flexure and the bladder with suture of the apertures was employed in 5 patients. One was completely cured, and in 2 a fecal fistula developed postoperatively, with, however, complete relief of vesical symptoms. The other 2 patients died. Even such simple procedures as colostomy and ileostomy were attended with poor results. Colostomy afforded complete relief of symptoms referable to the urinary tract in 1 patient, while another died at home of an unknown cause two months after operation. The patient subjected to ileostomy had fistulas involving the ileum, the sigmoid flexure and the bladder, and she succumbed at home postoperatively.

Primary repair and closure of the fistula were done on 1 of the patients with tuberculosis, and an excellent result was obtained. The second of these patients had been operated on elsewhere for the same condition, and although multiple procedures were employed here, he remained unimproved.

Postmortem studies were conducted on 11 patients in the entire series. The causes of death and the state of the kidneys are difficult to determine in the cases in the literature. Peritonitis accounted for the deaths of 7 of the 11 patients, 2 succumbed to bronchopneumonia,

1 to a hemorrhage on the twenty-fifth postoperative day and 1 to surgical shock. The kidneys were normal in 5 patients. Pyelonephritis was present in 2 patients, the renal pelvis were dilated in 1, and a fourth had a combination of dilated pelvis and enlarged kidneys. The latter condition alone was found in 2 patients.

Table 2 is a summary of results in the series reported by Sutton and in the present group.

The mortality demands some explanation. Included among these patients are those who had extensive carcinoma of the sigmoid flexure with involvement of the bladder and in whom it was deemed expedient to perform radical resection. The prognosis is extremely poor in such cases. Also included in this group are those patients who were subjected to secondary operations necessary for the alleviation of rather severe inflammatory conditions of the abdomen. Very important is the fact that most of these patients were in the fifth, the sixth and even

TABLE 2—*End Results in Eighty-Eight Cases of Surgically Treated Sigmoidovesical Fistula*

Cured	35
Sigmoidovesical fistula cured, but fecal fistula remained	7
Improved	5
Unimproved	4
Recurrence	4
Deaths	
Attributable to primary disease or operation for correction	26
Attributable to unrelated cause	1
Attributable to unknown cause	2
End result unknown	4

the seventh decade of life. The mortality from any operation in the period between 50 and 70 years of age is considerably enhanced, and procedures for the cure of sigmoidovesical fistula are no exception. However, the plight of this unfortunate group of persons is so miserable that one is forced to heroic measures to alleviate their distress.

CONCLUSIONS

- 1 Diverticulitis with perforation is perhaps the leading factor in the production of sigmoidovesical fistula.
- 2 The formation of a fistula is an extremely serious complication in patients with diverticulitis or other inflammatory conditions.
- 3 The mortality from one stage surgical procedures for correction of fistula due to diverticulitis is excessive.
- 4 With the facts learned from other surgical procedures on the bowel in mind, multiple stage operations are most satisfactory in dealing with this particular type of fistula. Colostomy which obviates spilling

from the upper into the lower part of the colon is usually the first stage, and it should be performed as close to the fistula as is practicable, to avoid redundant bowel above the vesicocolonic tract

5 A sufficient interval should be permitted to elapse after preliminary colostomy to allow spontaneous healing of the fistula to occur if it will. If it does occur, the colonic stoma should not be closed until one is positive that the inflammation in the sigmoid flexure has completely subsided, otherwise there will be a recurrence.

6 When carcinomatous invasion from the sigmoid flexure of the colon into the bladder has occurred and a sigmoidovesical fistula has formed, the prognosis is extremely poor.

7 Ascending infections of the urinary tract are not common complications of vesicosigmoidal fistula.

CLINICAL USE OF A SYNTHETIC SUBSTANCE RESEMBLING VITAMIN K (2-METHYL-1, 4-NAPHTHOQUINONE)

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In 1939, McKee and Doisy and their co-workers¹ showed that vitamin K has a quinoid structure. This led to investigation of the anti-hemorrhagic value in cases of experimental hypoprothrombinemia of many of the quinones. Of those examined, the 2-methyl-1,4-naphthoquinone and the 2-methyl-3-hydroxy-1,4-naphthoquinone possessed the greatest antihemorrhagic activity.² Rhoads and Fliegelman³ have recently reported favorable results in the control of hypoprothrombinemia in the human patient by the use of 2-methyl-1,4-naphthoquinone. Binkley, Doisy and others⁴ and Feiser⁵ have recently shown that 2-methyl-3-phytyl-1,4-naphthoquinone and the natural vitamin K possess identical physical properties and the same empirical formula.

PRESENTATION OF DATA

In this paper are presented 10 cases of clinical hypoprothrombinemia of various causes and the responses of the patients to administration of

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This work has been aided by grants from the Douglas Smith Foundation for Medical Research of the University of Chicago

1 McKee, R W, Binkley, S B, MacCorquodale, D W, Thayer, S A, and Doisy, E A. The Isolation of Vitamins K₁ and K₂, J Am Chem Soc **61** 1295 (May) 1939

2 (a) Ansbacher, S, and Fernholz, E. Simple Compounds with Vitamin K Activity, J Am Chem Soc **61** 1924 (July) 1939 (b) Almquist, H J, and Klose, A A. The Anti-Hemorrhagic Activity of Certain Naphthoquinones, *ibid* **61** 1923 (July) 1939 (c) Thayer, S A, Cheney, L C, Binkley, S B, MacCorquodale, D W, and Doisy, E A. Vitamin K Activity of Some Quinones, *ibid* **61** 1932 (July) 1939

3 Rhoads, J E, and Fliegelman, M T. The Use of 2-Methyl-1,4-Naphthoquinone in the Treatment of Prothrombin Deficiency in Patients, I A M A **114** 400-401 (Feb 3) 1940

4 Binkley, S B, Cheney, L C, Holcomb, W F, McKee, R W, Thayer, S A, MacCorquodale, D W, and Doisy, E A. The Constitution and Synthesis of Vitamin K₁, J Am Chem Soc **61** 2558 (Aug) 1939

5 Feiser, L F. Identity of Synthetic 2-Methyl-3-Phytyl-1,4-Naphthoquinone and Vitamin K₁, J Am Chem Soc **61** 2561 (Aug) 1939

2-methyl-1,4-naphthoquinone. These cases are summarized in the accompanying table. Daily studies of the plasma prothrombin were made for each patient while he was receiving the drug. The prothrombin times were determined at 37 C., a modification of Quick's method being used and the prothrombin time of normal human plasma being employed as the standard. In all cases the value for plasma fibrinogen was normal. Each patient was given 0.325 Gm. of bile salts with each 2 mg. of

Summary of Ten Cases

Case	Diagnosis	Prothrombin Time (Per Cent of Normal)			Treatment		Comment
		Before Therapy	24 Hrs. After Therapy Began	End of Therapy	Total Amount, Mg.	Number Days Treated	
1	Stricture of common duct	15	100	100	40	5	Bleeding gums and menorrhagia both ceased within 8 hours after beginning treatment
2	Common duct stone	65	100	100	32	4	
3	Carcinoma of head of pancreas	75	100	100	24	3	
4	Obstructive jaundice from adhesive band across common duct	53	100	100	24	3	
5	Biliary fistula	54	100	100	32	3	
6	Nontropical sprue	24	32	100	128	16	Normal prothrombin time not obtained until the 16th day
7	Hepatitis	60	50	100	60	5	Vomited and did not retain vitamin K 48 hours after I V vitamin K; prothrombin time was normal
8	Acute yellow atrophy	23	33	66	48	6	Died on 8th day in coma
9	Cirrhosis	50	50	38	140	14	Bile in stools
10	Cirrhosis	28	32	38	40	5	Bile in stools

2-methyl-1,4-naphthoquinone except those in cases 7 and 9, who also received a water-soluble sulfonated derivative of this naphthoquinone⁶

The typical response to this naphthoquinone is graphically illustrated in chart 1 (case 1). The patient was bleeding from the gingival margins and had many cutaneous ecchymoses associated with obstructive jaundice. Eight hours after the first administration of this drug the bleeding ceased and no more ecchymoses appeared. In chart 2 (case 9) is shown the failure of this substance to increase a reduced level of plasma prothrombin in a case of advanced cirrhosis of the liver. As will be

⁶ The oral preparation of 2-methyl-1,4-naphthoquinone and the bile salts (bilon) were supplied by Eli Lilly & Co. The sulfonated water-soluble preparation was supplied by the Abbott Pharmaceutical Laboratories.

noted in the chart, daily oral doses of this substance failed to improve the prothrombin time. On the thirteenth day of treatment the intravenous route was substituted, 12 mg of the aqueous-soluble substance being given without effect.

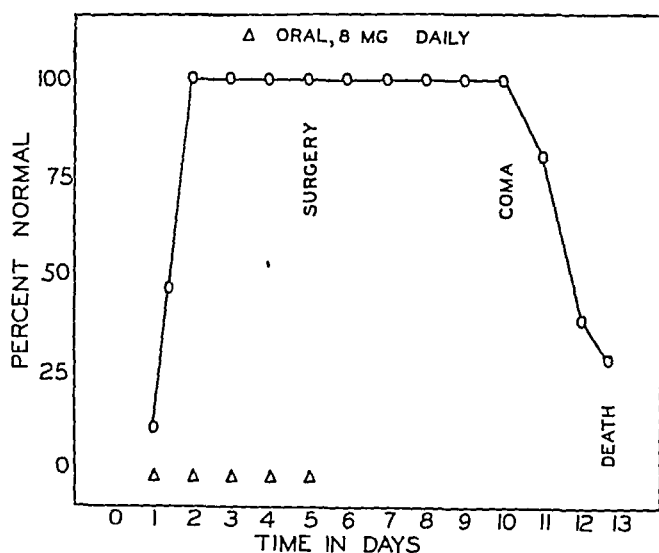


Chart 1 (case 1) —Record in a case of stricture of the common bile duct

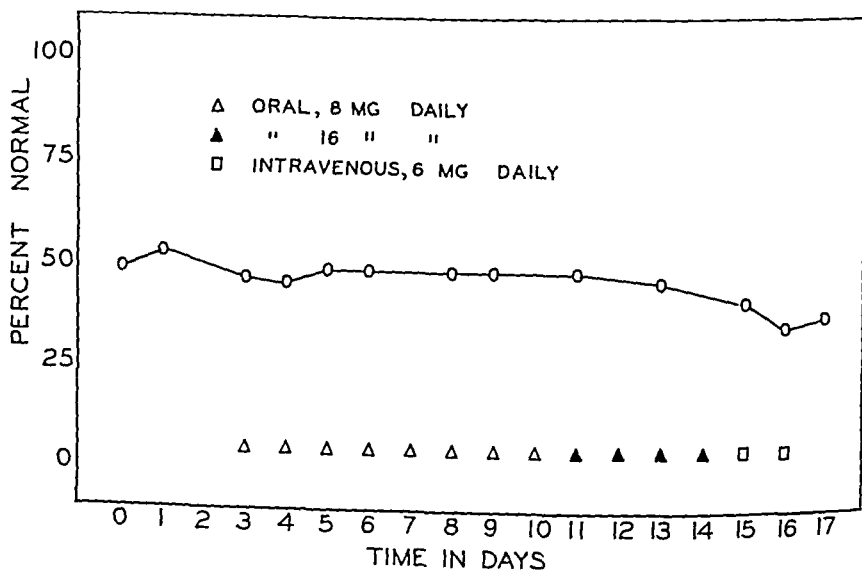


Chart 2 (case 9) —Record in a case of cirrhosis of the liver

COMMENT

These cases present three types of response to the naphthoquinone. The first is that seen in cases 1, 2, 3, 4 and 5, in which the prothrombin rapidly returned to normal levels. In each of these cases the low level

of plasma prothrombin was produced by defective absorption of vitamin K, attributable to the absence of bile in the intestinal tract. When this absorption defect was corrected by oral administration of bile salts, the prothrombin rapidly returned to normal when the naphthoquinone was given.

The low level of plasma prothrombin in the patient with nontropical sprue (case 6) is a manifestation of inadequate absorption of vitamin K together with other fat-soluble substances. The sluggish type of response seen in this case might have been expected since the concentration of the vitamin in the intestinal tract was increased without any change in the fundamental absorption defect. In two previous studies on this patient similar responses were observed when the alfalfa concentrate was given.

In cases 9 and 10 no appreciable change in the prothrombin time was produced by the naphthoquinone. The patients in both of these cases had far advanced cirrhosis of the liver associated with chronic alcoholism. Bile salts were given with the 2-methyl-1, 4-naphthoquinone, although adequate bile was already present in the stools of both patients. In case 9, after twelve days of therapy, during which time 128 mg. of the naphthoquinone was given orally, the water-soluble sulfonated derivative of the naphthoquinone was given in two doses of 6 mg. each by vein. This assured the presence of the preparation in the circulation, but even under these conditions the prothrombin time did not improve. The failure of the plasma to respond in these cases suggests that in the presence of advanced hepatic cirrhosis the process of activation of prothrombin by the naphthoquinone may be impaired.

None of the patients studied showed any symptoms of untoward reaction or toxic symptoms which might be ascribed to this drug. All patients received at least 8 mg. of this substance daily, while those in cases 7 and 9 received as much as 16 mg. daily for two and four days respectively. The patient in case 9 received a total of 140 mg. of naphthoquinone over a sixteen-day period, without ill effects. Occasional nausea was observed, but this was not present if the bile salts were omitted in a test dose. However, until further clinical data are at hand the naphthoquinones should not be used unless the patient can be carefully observed.

The results obtained with naphthoquinone in these patients compare favorably with the results obtained in this clinic in prothrombin-deficient patients receiving the vitamin K concentrate. However, there is considerable variance of opinion as to the relative antihemorrhagic values of the alfalfa concentrate and the synthetic naphthoquinones in the case of the experimental animal. It is generally agreed that the 2-methyl-1, 4-naphthoquinone and the 2-methyl-3-hydroxy-1, 4-naphthoquinone have a high degree of activity, the former possessing more activity than the latter. Ansbacher and Fernholz^{2a} stated the belief that the 2-methyl-1,

4-naphthoquinone is as active as the natural vitamin, while Almquist and Klose ^{2b} stated that this synthetic preparation is considerably less potent than the concentrate. However, until it is possible to assay pure natural vitamin K in terms of its naphthoquinone content, no accurate comparisons can be made between this natural vitamin and the synthetic preparations.

SUMMARY

Ten patients with low levels of plasma prothrombin were given synthetic 2-methyl-1,4-naphthoquinone, and their responses were recorded.

The failure of prothrombin response in 2 cases of advanced cirrhosis of the liver is discussed.

No evidence of toxicity was observed during administration of this substance.

Dr. Lester R. Dragstedt gave helpful advice and valuable criticism in the preparation of this paper.

REGIONAL AND GENERAL TEMPERATURE RESPONSE FOLLOWING EXPERIMENTALLY INDUCED ACUTE INFLAMMATION AND INFECTION

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In the course of experimental work on surgical infections it seemed necessary to study anew the temperature responses of the body to acute inflammations and infections. For our own purposes it was desirable to observe the relation between the deep temperatures of the brain, liver, rectum and muscles in the normal subject, the variations in deep temperature as influenced by the commonly used anesthetic drugs, the time of appearance of elevation of temperature in the tissues involved and in the intra-abdominal organs and the brain after production of an acute localized inflammation, the reliability of the rectal temperature as a guide to the febrile state of the subject, and the relation between leukocytic response and elevation of temperature. Observations of this sort have, of course, repeatedly been made, but such observations and their interpretations as published in the literature have varied greatly. As a preliminary study it appeared desirable to become familiar with and to standardize the methods available to us and to make certain observations of our own under conditions obtained in our laboratory. The preliminary observations are reported here.

APPARATUS AND METHODS OF OBSERVATION

The particular assembly used in the experiments herein reported was one having a portable potentiometric temperature indicator,¹ five needle style thermocouples and a rotary thermocouple switch. The temperature range for the assembly was from -4 to 50°C . The thermocouples² were made from no. 20 Stubbs gage needles of platinum-iridium shafts and bakelite handles with no. 14 iron-constantan duplex lead wires. These thermocouples can be sterilized by boiling in water. The assembly was so arranged that it was possible to take temperature readings at five

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¹ No. 8663, Leeds and Northrup Company, Philadelphia

² These thermocouples were constructed by the Leeds and Northrup Company, Philadelphia

different parts of the body of the experimental animal within one minute. This apparatus has an estimated accuracy within 0.005 degree (C).

Dogs were used in these experiments. For observations of the temperature of the brain, the animals were prepared by preliminary trephining of the temporal bone, the opening being uniformly placed over the midparietal region of the cerebral cortex. For observations of the temperature of the liver, a preliminary operation was done, a rib over the right lower lateral aspect of the thorax was resected, and the costophrenic sulcus was obliterated by suturing the diaphragmatic to the parietal pleura. Animals were not used for experimentation until seven days after the operation, at which time the wounds were healed. The needle style thermocouples were inserted to a depth of 2 cm. into the subcortical substance of the brain and held securely in place by means of a rubber flange fastened to the scalp with adhesive tape. The couples were inserted into the substance of the liver to a depth of 5 cm. and anchored in the same fashion. The rectal temperature readings were made by inserting a thermocouple into the ampulla of the rectum for a distance of 5 cm. The temperatures of the muscles were determined by inserting a thermocouple for a distance of 5 cm. obliquely into the muscles of the thigh on the outer aspect of the leg. Readings were made at all points every two, five or ten minutes, according to the plan of the experiment. The thermocouples were regularly checked with a series of finely graded mercury thermometers. The temperature of the room was not allowed to vary over 3 degrees (C), and wind currents were excluded. The humidity of the room was recorded in volumes per cent by polymeter (Lambrecht's). During the experiments, many of which were carried on for twenty-four hours, no attempt was made to supply nourishment to the experimental animal or to replace the loss of fluid from the body.

NARCOSIS AND ANESTHESIA

In experiments 1 to 5, observations were made on deep temperatures in dogs after morphine medication and the use of certain anesthetic drugs. All experiments were of two hours' duration. Thermocouples were inserted in the liver, the rectum and (in experiment 5) the brain. Readings were made every two minutes. The room temperature was 25 to 26 C. The humidity was 35 to 40 volumes per cent.

EXPERIMENT 1—A dog weighing 11.6 Kg. was given 0.01 Gm. of morphine intramuscularly. Anesthesia was not used. At the beginning of the experiment the temperature of the liver and that of the rectum were the same, but the former quickly fell below the latter, and this relation between the two temperatures persisted. Both showed a gradual decrease. Twenty-four minutes after the start of the experiment the temperature of the liver reached a constant of 37.2 C., the rectal temperature continued to drop and did not reach a constant until forty-eight minutes had elapsed. From this point the two temperatures were within 0.5 degree (C) of each other. Ice applied to the head for eleven minutes was not followed by a demonstrable change in the temperature of either the rectum or the liver. Ice compresses applied to the abdomen for twenty-one minutes caused a rapid drop of 0.7 degree (C) in the temperature of the liver. The temperature of the rectum did not fall until four minutes later and dropped only 0.5 degree (C). After removal of the cold application both temperatures rose, the temperature of the rectum returned to 37 C., and that of the liver rose to 36.8 C. toward the end of the experiment.

EXPERIMENT 2 (*Amytal Sleep*)—A dog weighing 12 Kg was given 11 Gm of amytal intraperitoneally. Fifteen minutes afterward the temperature of the liver and that of the rectum were approximately equal, at 38.6 C. Both began to fall immediately, that of the liver more rapidly than that of the rectum. The fall continued for thirty minutes, after which both values became fairly constant. Throughout the remainder of the two hours both remained constant, that of the liver at 37.8 C and that of the rectum at 37.9 to 37.95 C.

EXPERIMENT 3 (*Spinal Anesthesia*)—A dog weighing 13 Kg was anesthetized with 50 mg of procaine hydrochloride given into the subarachnoid space at the level of the second lumbar vertebra. Immediate paralysis of both hindlegs resulted. The first temperature observation was taken three minutes after the onset of paralysis of the hindlegs. The temperature was 39.5 C (temperature before anesthesia, 37.4 C). It rose rapidly to a peak at 40.2 C and dropped slowly after thirty minutes. As the effect of the anesthetic wore off, the rectal temperature reached a "low" of 39.2 C, at which point the experiment was abandoned because of muscular activity of the lower extremities of the animal.

EXPERIMENT 4 (*Avertin Anesthesia*)—A dog weighing 13.6 Kg was anesthetized with 80 mg of avertin in amylene hydrate per kilogram of body weight, administered by rectum. The rectal temperature was observed to hold a slightly higher level than that of the liver throughout. The temperature of the rectum was 38 C at first and fell gradually to 37.8 C. That of the liver was 37.9 C and fell gradually to 37.6 C.

EXPERIMENT 5 (*Amytal Sleep*)—A dog weighing 13.6 Kg was given 0.8 Gm of amytal intraperitoneally. The temperatures of the liver, brain and rectum stayed between 37.5 and 39 C, and all these were closely parallel as they slowly dropped through the two hours. The deep cerebral temperature was highest, the temperature of the liver was intermediate and the rectal temperature was lowest.

INFLAMMATION

In experiments 6 to 10, observations were made on the deep temperatures and on the leukocytic reaction in dogs after production of a localized acute aseptic inflammation by means of sterilized turpentine-paraffin solution. All except experiment 10 were of twenty-four hours' duration, readings being taken every ten minutes. Thermocouples were inserted in the brain, the liver, the rectum and the muscles of the thighs. The room temperatures ranged from 24 to 28 C. The humidity was from 25 to 35 volumes per cent.

EXPERIMENT 6—A dog weighing 12 Kg was given 11 Gm of amytal intraperitoneally. The temperatures of the liver, rectum and brain underwent similar variations, but their relation to each other was not constant. At the start of the experiment the rectal temperature was 38.8 C. At this level it was slightly higher than that of the brain or the liver. However, after three hours the temperature of the liver became highest and remained so throughout the twenty-four hour period. Up to twelve hours there was a gradual rise in all three deep temperatures, this rise giving to the curves a sloping apex, followed in the second twelve hours by a decline to meet, approximately, the readings recorded at the start of the period. The temperature of the muscles of the left leg was higher at the start (34.5 C) than that of the right leg. This relation reversed itself several times as the

experiment progressed. The leukocyte count, starting at 19,500 per cubic millimeter, rose irregularly to 23,000 at the end of nineteen hours, then dropped to 20,000. The maximal leukocytosis occurred later than did the maximal rise in deep temperatures of the liver, rectum and brain. This experiment was planned as a control for experiments 7 to 10.

EXPERIMENT 7—A dog weighing 11 Kg. was given 0.74 Gm. of amytal intraperitoneally. In this experiment a localized inflammatory process was initiated in the muscles of the right thigh by the injection of 6 cc. of a turpentine-paraffin solution (prepared by heating a mixture of 2 parts paraffin and 1 part turpentine, by volume), which had been sterilized and cooled to 30.5 C., into the area where the thermocouple was inserted into the tissue. The injection was followed by a rise in muscular temperature of over 7 degrees (C.). This rise manifested itself uninterruptedly in the course of four hours, rapidly at first, then less rapidly. Associated with the rise in peripheral temperature there was a sharp elevation of the temperatures of the liver, rectum and brain and an increase in the leukocyte count from 7,000 to 25,000 per cubic millimeter. As the temperature of the peripheral area dropped through the next twenty hours to reach the approximate level at which readings had been made before the injection, the tissue temperatures in the liver, the rectum and the brain continued to ascend, and the leukocyte count remained elevated.

EXPERIMENT 8—A dog weighing 12.4 Kg. was given 0.74 Gm. of amytal intraperitoneally. In this experiment a localized inflammatory process was initiated in the muscles of the left thigh by injection of 6 cc. of turpentine-paraffin solution, sterilized and cooled to 35 C., approximately at the point where the thermocouple had been inserted. There was a rapid rise in temperature of the muscles of the thigh, the rise was only 2 degrees (C.), but the level to which it brought the temperature was the same as in experiment 7 (37 C.). The temperatures of the intracranial and intra-abdominal organs showed a gradual and steady elevation.

In the last twelve hours of this experiment the temperature of the inflamed area (musculature of the left thigh) remained elevated and did not drop as it did in the same period in the preceding experiment. Again the relation of the temperatures of the liver, rectum and brain to each other was unaffected by the peripheral inflammatory process.

EXPERIMENT 9—A dog weighing 11.8 Kg. was given 0.74 Gm. of amytal intraperitoneally. In this experiment 6 cc. of a turpentine-paraffin solution (sterilized and cooled to 37 C.) was injected into the musculature of the right thigh. The behavior of the temperatures of the tissues of the leg was roughly similar to that observed in experiments 7 and 8. The affected leg showed a rise in temperature following the injection, which was maintained persistently throughout the twenty-four hour period at a point averaging 1.5 degrees (C.) above that of the unaffected extremity. The temperatures of the intracranial and intra-abdominal organs again exhibited a persistent elevation. The leukocyte count, which rose from 11,000 to 16,800 per cubic millimeter, exhibited a curve which closely paralleled that shown in experiment 7.

EXPERIMENT 10—A dog weighing 17.5 Kg. was given 1.1 Gm. of amytal intraperitoneally. When the temperatures of the tissues had reached a fairly constant level (one hour after the observations were started), the dog was placed in an especially constructed cabinet which covered the body from the upper part of the abdomen down to and including the feet. The cabinet was made of wood, its sides having glass windows for observation. The extensions of the couples passed through rubber-stoppered openings in the sides of the cabinet. The cabinet was

heated by incandescent bulbs. The temperature within the cabinet was purposely maintained at a higher level than any of the peripheral temperatures observed in the previous experiments, an attempt being made to determine whether the temperature of an inflamed area might rise above that of the environment. After the animal was placed in the cabinet, all the tissue temperatures rose. After one hour and twenty minutes an inflammatory process was initiated in the tissues of the right thigh by injection of a mixture of turpentine and paraffin, prepared as in the earlier experiments. The temperatures of the brain, liver and rectum did not exceed that of the air of the cabinet. The upward trend of the peripheral temperature of the right thigh, which was apparently induced by placing the animal in the heated cabinet, was not affected by injection of the inflammatory agent.

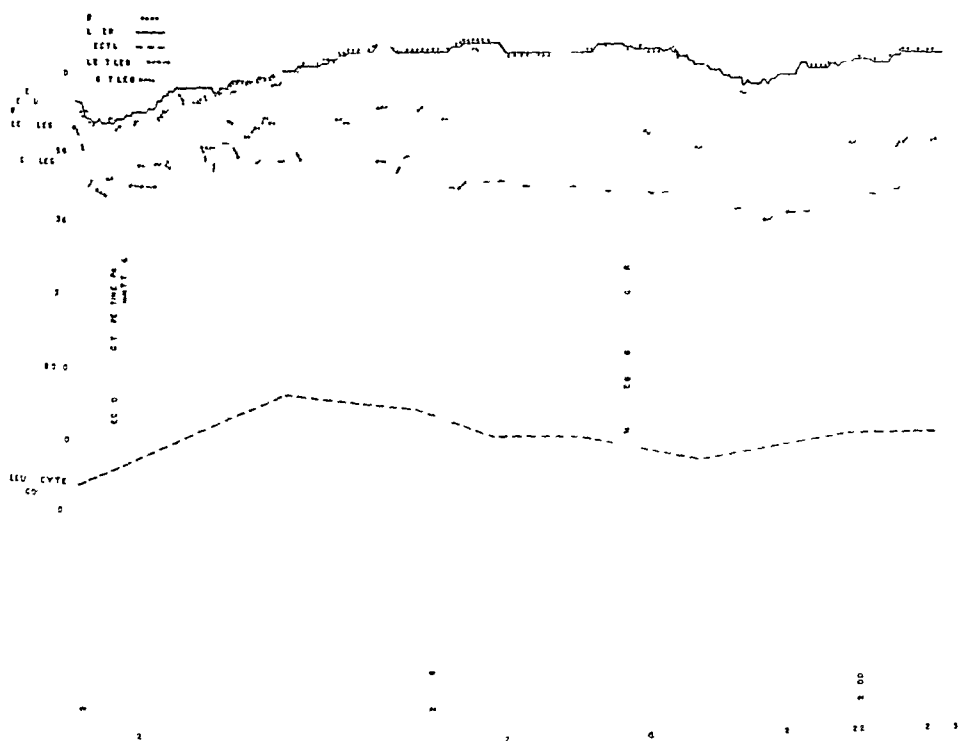


Chart 1—Data on experiment 9 Six cubic centimeters of amytal was administered

INFECTION

In experiments 11 to 15 observations were made on the deep temperature and on the leukocytic response after production of a localized acute infection. All experiments were of twenty-four hours' duration, readings were made every ten minutes. Thermocouples were placed in the brain, the liver, the rectum and the muscles of the thighs. The room temperature was 24 to 28 C. The humidity was 20 to 40 volumes per cent.

EXPERIMENT 11—A dog weighing 12.5 Kg. was given 0.8 Gm. of amytal intraperitoneally. The temperatures of the deep organs were not unusual in their

behavior in comparison with the readings obtained in earlier experiments. One-half hour after the thermocouples had been placed, 3 cc of a broth suspension (containing 2,000,000,000 organisms to a cubic centimeter) of *Staph aureus* was injected into the muscles of the right thigh, approximately at the point to which the thermocouple had been inserted. There was an immediate rise in the regional temperature from 31 to 35 C. This was followed by a drop, and the higher level was not approached again until three hours later. The maximal elevation of the white blood cell count occurred seventeen hours after injection of the organisms.

EXPERIMENT 12—A dog weighing 115 Kg was given 0.8 Gm of amytal intraperitoneally. In this experiment the technic was exactly the same as in the

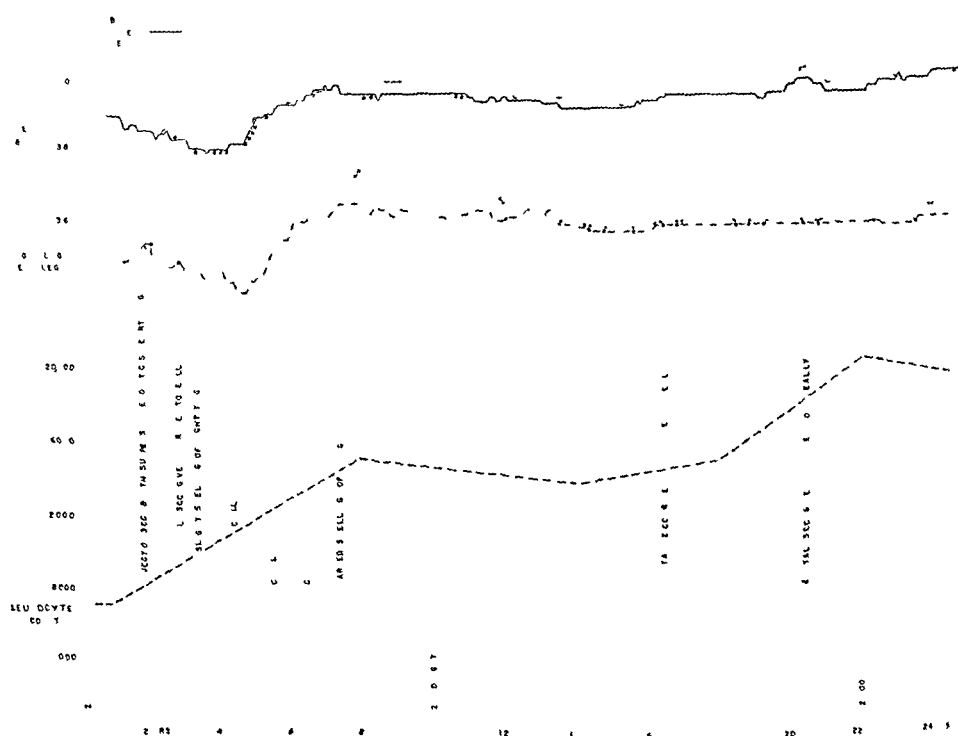


Chart 2—Data on experiment 15

preceding one (experiment 11), except that 6 cc of a broth suspension (about 2,000,000,000 organisms per cubic centimeter) of *Staph aureus* was injected into the muscles of the right thigh. The temperature curves were similar to those of the preceding experiment. The muscular temperature of the infected leg was elevated above that of the normal leg for nine hours then fell to a lower level. The systemic temperatures as measured in the brain, liver and rectum showed a persistent rise. The leukocyte count reached its maximum later than it did in the experiments dealing with acute inflammation. It rose from 9,000 to 26,000 per cubic millimeter in ten hours.

EXPERIMENT 13—A dog weighing 13 Kg was given 0.8 Gm of amytal intraperitoneally. In this experiment 6 cc of a suspension of *Staph aureus* in whole blood (about 2,000,000,000 organisms to the cubic centimeter) was injected into

the right thigh. In comparison with the 2 earlier experiments (11 and 12) it was observed that the deep temperatures were higher, reaching 41.4 C. Similarly, the regional temperature in the infected leg reached 38.8 C, a level which was 1.5 degrees higher than the highest peripheral temperature observed in experiments 11 and 12. The leukocyte count rose slowly from 11,000 per cubic millimeter to a peak of 21,800, which was reached sixteen hours after the injection.

EXPERIMENT 14—A dog weighing 14 Kg. was given 0.9 Gm. of amytal intraperitoneally. Six cubic centimeters of a saline suspension of *Staphylococcus* (about 2,000,000,000 organisms to the cubic centimeter) was injected into the muscular tissues about the point of the thermocouple inserted into the right thigh. The peripheral temperature (muscle of the right thigh) reached a height greater than had been previously observed, 39.4 C, keeping pace with the elevation in deep temperatures (brain, liver, rectum) to 41 C. The leukocyte count rose from 7,000 to 25,000 per cubic millimeter after twenty-one and one-half hours.

EXPERIMENT 15—A dog weighing 15.5 Kg. was given 1 Gm. of amytal intraperitoneally. Three cubic centimeters of a broth suspension of beta hemolytic streptococcus (about 2,000,000,000 organisms to the cubic centimeter) was injected into the muscles of the right thigh of the animal about the point of the thermocouple. There was a distinct rise in the deep temperatures after the injection. This was irregularly maintained throughout the twenty-four hour period. The initial rise of the temperature in the muscles of the infected thigh after the injection was followed by an elevation which persisted for twelve hours. The temperature of the leg then dropped to approximately that of the outer extremity. The leukocyte count slowly rose from the starting point of 7,000 per cubic millimeter to a peak of 20,400 at the twenty-second hour. The drop in peripheral temperature at the site of infection was concomitant with the occurrence of signs of edema at that area.

SUMMARY AND COMMENT

Detailed report is made of observations on deep tissue temperatures as affected by experimentally induced inflammation and infection in a series of 15 experiments. In 9 of these, observations were made over a twenty-four hour period. The first 5 experiments were planned to give information as to the normal variations of the temperatures of these parts (liver, brain, rectum, muscles) after several anesthetic agents were administered. Evidence is presented that amytal introduced into the peritoneal cavity gives a very satisfactory control of the animals for this type of experimental study. The deep temperatures were more constant after administration of amytal than after administration of morphine, avertin with amylene hydrate or procaine hydrochloride. Amytal was, therefore, selected as the anesthetic of choice for the experiments. It was found that variations of 0.5 degree centigrade in the temperature of the liver, brain or rectum were common and of no significance, the highest temperature or the lowest temperature being exhibited by any one of the organs at different times. It was also found that a variation of 1 degree centigrade in temperature of the room was without effect on the temperatures of the deep organs or tissues.

From a study of the experiments (6 to 10) dealing with aseptic inflammation the following inferences may be drawn

1 Injection of an inflammatory agent into the muscular tissues of the periphery is accompanied by an immediate rise in local temperature

2 Production of an acute peripheral inflammation is followed within a few hours by an increase in the deep temperatures as measured in the liver, brain and rectum

3 The peripheral temperature at the site of the localized inflammation may decline as swelling develops at the site, although the deep temperatures continue to rise or remain elevated

4 The leukocyte count shows a steady increase during the first ten to twenty hours after the production of an acute localized peripheral inflammation, its maximum not being reached until a varying number of hours after the peak of the peripheral temperature

5 In the first twenty-four hours after the initiation of an acute localized peripheral inflammation the temperature of the infected area does not exceed that of the deep organs (liver, brain, rectum)

It is further indicated by experiment 10 that a peripheral inflammation does not cause an increase in local temperature in an extremity previously subjected to increase in temperature by inclusion in a heated cabinet. In the experiment referred to, the temperature of the tissues in which inflammation was to be induced had shown a significant elevation after the posterior extremities of the animal were placed in a heated cabinet. In none of the experiments recorded herein did the local temperature at the site of acute inflammation at any time exceed that of the deep organs. This observation leads to the impression that elevation of the temperature of peripheral tissues in association with acute inflammation is due chiefly to the induced hyperemia rather than to specific biochemical or metabolic processes at work in the area of cellular change. It is recognized, however, that this evidence is hardly sufficient to rule out the factor of local increase in metabolism of tissue as a cause of heat production.

The frequency of readings in the experiments reported affords information as to the order and sequence of the rise in temperature of the organs and tissues in which observations were made. The variations observed in the rise in temperature of the muscles of the leg in the different experiments, these having been carried out with the same technic in all cases, are not easily explained, nor are the variations in the degree of leukocytosis and in the time at which there was maximal leukocytosis. Attention is called to the fact that the value of the observations reported here lies in the comparative study of the relation of the abnormal temperatures of the disturbed peripheral tissues to

those of similar tissues and to the temperatures of the deep intracranial and intra-abdominal organs, both in the degree of heat production and in the rate of its development. It is pointed out further by these observations that the fluctuations in temperature of an acutely inflamed peripheral zone do not parallel the rise in general temperature of the body as measured in the internal organs (brain, liver, rectum). That the elevated temperature in these organs remains persistently at a higher level than those of the inflamed region suggests that since, in the process of circulation, the blood passes through the intra-abdominal organs before being transferred to the periphery, the increased warmth of the inflamed area is due not to local production of heat but to transference of heat to the area by the increased rate of flow of blood (hyperemia). This impression was obtained in working with inflammatory processes (experiments 6 to 10) and also with infection (experiments 11 to 15).

In brief summation of the experiments dealing with infection (experiments 11 to 15) it may be concluded that

- 1 Injection of an infectious agent into the muscular tissues of the periphery is accompanied by an immediate rise in local temperature, this rise being, in general, higher than that observed in the experiments dealing with sterile inflammation

- 2 Production of an acute peripheral infection is followed within a few hours by a rise in the temperatures of the deep organs, just as observed in the experiments dealing with inflammation

- 3 In the twenty-four hour period immediately following initiation of the infection the temperature in the infected zone rises and then falls when suspensions of staphylococci are injected. The peripheral temperature is maintained at a higher level when suspensions of streptococci are injected. The deep temperatures continued to rise or remain elevated throughout the period of observation just as in the experiments in sterile inflammation

- 4 Leukocytosis is not maximal as early after the production of an acute infection as after the start of an acute inflammation

- 5 After the initiation of an acute localized peripheral infection, the temperature of the infected area does not exceed that of the deep organs

- 6 The regional and general responses of temperature after an acute infection has been produced are not appreciably different when the organisms are suspended in physiologic solution of sodium chloride, broth or whole blood

A comparison of these findings with those of other investigators may be made. The work of Maximov,³ who demonstrated by a series of

³ Maximov, cited by Segale, M. Temperature of Acutely Inflamed Tissues, *J. Exper. Med.* 29:235, 1919

accurate temperature determinations carried out with thermoelectric batteries that in no part of the inflammatory process is the temperature higher than that of the heart's blood or the blood of the larger vessels is confirmed by these observations. Similarly, the contention of Jacobson,⁴ Bernard,⁵ Schneider,⁶ and Ruppert,⁷ namely, that if the inflamed area has a higher temperature than that of the corresponding area, it cannot be asserted that its temperature is above that of the central blood, is confirmed. Marchand,⁸ in a summary of the results of a study of this subject, concluded that the increased flow of blood is the responsible factor in heat production, rather than a disturbing element. It was suggested by Bernard that the flow of blood to a part might be considered the result of local calorification. After exhaustive thermometry studies, in which it was demonstrated that the temperature of the blood in the hepatic vein is consistently warmer than that in the portal vein, he (Bernard) came to the conclusion that the blood actually is warmed by certain organs but that there is no one organ which generates heat, it is a function of all tissues which are subject to nutrition. Cavazzani⁹ recorded an increase in temperature of the hepatic parenchyma after blocking the circulation in the hepatic artery and portal vein. Segale,¹⁰ supporting Cavazzani's work, reported 6 animal experiments in which the temperature in the inflamed area was observed to rise after the production of ischemia in the part or after the death of the animal. Krehl and Kratzsch¹¹ found that in animals with fever the liver is as warm as in normal animals or warmer. Schade, Haagen and Schmidt,¹² in disputing Marchand's belief that the increased local heat in inflamed tissue is due to the afflux of blood to the affected part, demonstrated that the temperature of the inflamed area rose 0.1 degree

4 Jacobson, H. Ueber normale und pathologische Temperaturen, *Virchows Arch f path Anat* **51** 275, 1870

5 Bernard, C. Leçons sur la chaleur animale, sur les effets de la chaleur et sur la fièvre, Paris, J. B. Baillière, 1876

6 Schneider, O. Einige Beobachtungen über den Stoffwechsel bei künstlicher Plethora und Anämie, Marburg, C. L. Pfeil, 1861

7 Ruppert, M., cited by Segale¹⁰

8 Marchand, F. Die thermischen Krankheitsursachen, in Krehl, L., and Marchand, F. *Handbuch der allgemeinen Pathologie*, Leipzig, S. Hirzel, 1908, vol 1, chap 2

9 Cavazzani, E. Sul differenziamento degli organi della sensibilità termica de quelli del senso di pressione, *Riforma med* **8** (pt 1) 797-801, 1892

10 Segale, M. Temperature of Acutely Inflamed Peripheral Tissue, *J Exper Med* **29** 235, 1919

11 Krehl, L., and Kratzsch. Untersuchungen über die Orte der erhöhten Wärmeproduktion in Fieber, *Arch f exper Path* **41** 185, 1898

12 Schade, H., Haagen, W., and Schmidt, K. Thermoelektrische Messung der Wärmeverhältnisse an Ort der Entzündung, *Zentralbl f d ges exper Med* **83** 343 1936

above the rectal temperature. In the experiments of Schade, Haagen and Schmidt localized inflammation was produced by the injection of turpentine-paraffin solution twenty-four hours before the observations were made. In our own experiments the temperature of the inflamed area was not at any time found to be higher than that of the liver, brain and rectum.

In keeping with van't Hoff's law Shorr,¹³ working with tissues in vitro (Warburg technique) has observed a tremendous increase in tissue metabolism in the presence of infection. Similarly, Gessler¹⁴ concluded after extended experimental studies that the effect of external heat is a great increase in metabolism of tissue with subsequent hyperemia. In our experiments the degree of elevation of peripheral temperature has been greater in the experimental infections than in the inflammations. This is in keeping with Shorr's observation. There is, however, no conclusive evidence that increased metabolism is responsible for increased production of heat.

Returning again to the role of the circulating blood and its possible effect on the area of the increased temperature as a cooling or heating phenomenon, attention is called to the classic experiments of Ludwig and Spiess,¹⁵ confirmed by Burton-Opitz¹⁶ in which it was demonstrated that in cases of parotitis there are marked local heating and an elevation of temperature above that of the regional arterial blood, the venous blood being warmer than the arterial blood. Also, as has been mentioned, Schade made observations showing that the temperature at the site of the infection rose above that of the rectum. On the other hand, one of us (Conway¹⁷) has reported on regional temperatures in carbuncles in man. In only 2 of 20 cases was the temperature in the acutely inflamed zone even a fraction of a degree above the rectal temperature taken at the same time. Also, the regional temperatures in the infected areas were consistently higher in that portion of the carbuncle in which hyperemia was maximal.

The reports in the literature relating to temperatures in infected areas are few. To our knowledge, diurnal temperature readings following experimental inflammation and infection as recorded herein have not previously been made. All of the information made available

13 Shorr, E. Personal communication to the authors.

14 Gessler, H. Ueber Entzündung, Arch f exper Path u Pharmacol **163** 477, 1931.

15 Ludwig, C, and Spiess, A, cited by Segale¹⁰

16 Burton-Opitz, R. Ueber die Temperatur des Chorda- und des Sympathikusspeichels, Arch f d ges Physiol **97** 309, 1903.

17 Conway, H. Subcutaneous Temperatures in Localized Infections, Proc Soc Exper Biol & Med **34** 353, 1936.

through these experiments has supported, though not conclusively, the belief that the increase in local heat at the site of an acute inflammation or infection is occasioned by the warmth brought to the site by the increased afflux of blood. While the temperature of the circulating blood probably is dependent on cellular biochemical activity and metabolism in the tissues, there is nothing in the results of these experiments to indicate that these forces are augmented as producers of heat at the site of an acute localized inflammation or infection.

Dr M E Pickworth, of San Jose, Calif, assisted in the management of the experiments.

STUDIES IN THE ETIOLOGY OF ACUTE APPENDICITIS

AN INQUIRY INTO THE FACTORS INVOLVED IN THE DEVELOPMENT
OF ACUTE APPENDICITIS FOLLOWING EXPERIMENTAL
OBSTRUCTION OF THE APPENDICAL LUMEN
OF THE RABBIT

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AND

OWEN H WANGENSTEEN, M D

MINNEAPOLIS

PURPOSE OF THIS INVESTIGATION

The secretion of fluid by the appendix of man, the chimpanzee and the rabbit and the development of appendicitis consequent to obstruction of the appendical lumen in these species have been reported¹ Twenty-four other species of animals have failed to show either secretion of fluid or development of appendicitis following obstruction by ligation²

The rabbit has proved so useful an animal in which to study the effects of appendical obstruction that it is believed worth while to outline the results of the experiments which have been done on this species Further, it is possible in the rabbit, in which the functional behavior of the cecal appendage in many respects is not unlike that of the vermiform process of man, to make controlled observations which cannot

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These researches were supported by grants of the Graduate School of the University of Minnesota and by a grant for technical assistance by the Works Project Administration, Official Project 665-71-3-69, Subproject 258

1 (a) Wangensteen, O H , Buirge, R E , Dennis, C, and Ritchie, W P Studies in the Etiology of Acute Appendicitis The Significance of the Structure and Function of the Vermiform Appendix in the Genesis of Appendicitis, Ann Surg **106** 910, 1937 (b) Wangensteen, O H , and Dennis, C The Production of Experimental Acute Appendicitis (with Rupture) in Higher Apes by Luminal Obstruction, Surg, Gynec & Obst **70** 799, 1940 (c) Wangensteen, O H , and Dennis, C Experimental Proof of the Obstructive Origin of Appendicitis in Man, Ann Surg **110** 629, 1939

2 Dennis, C , Buirge, R E , and Wangensteen, O H An Inquiry into the Functional Capacity of the Cecal Appendage in Representative Birds and Mammals, Surgery **7** 372, 1940

be done on man, and such observations also are of the greatest value in promoting understanding of the effects of luminal obstruction of the appendix of man. It is the special object of this paper to indicate the extent of the secretory capacity of the cecal appendage of the rabbit, the effects of obstruction and the factors which alter secretory capacity and the effects of obstruction.

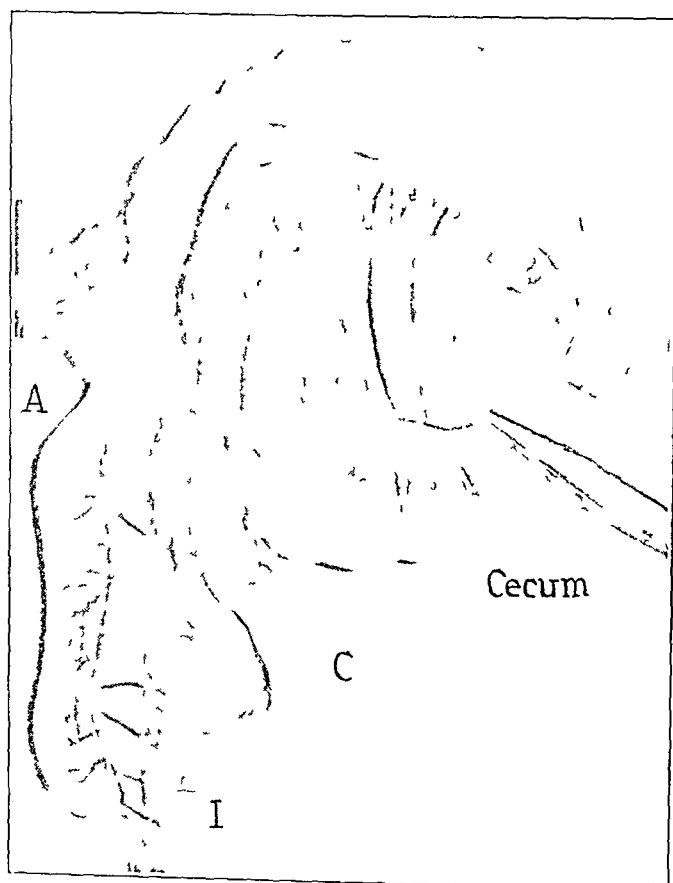


Fig 1—Photograph of the normal cecum and adjacent structures of the rabbit. The cecal pouch is very thin walled, coiled, about 30 cm long and in its widest diameter roughly 6 cm, at the distal end it is capped by the cecal appendage (A), which is sharply demarcated from the gray-green cecum by its reddish yellow color and the lymphoid follicles which show through the thin muscularis and serosa. The appendage has an average length of 6 to 9 cm. The blood supply comes from the superior mesenteric vessels, a part passes down near the appendage in the mesentery, and the rest comes across the mesentery in a dozen vessels from the ileum (I). C, colon. A forceps is placed on the ileocecal valve.

MATERIALS

Two hundred and thirty-five rabbits were used in the experiments reported here. The cecal pouch of the rabbit is very thin walled, about 30 cm long and in its widest diameter roughly 6 cm wide, at the distal end it is capped by the cecal appendage, or appendix, which is sharply demarcated from the gray-green cecum

by its reddish yellow color and the lymphoid follicles which show through the thin muscularis and serosa. The appendage (fig 1) has an average length of 6 to 9 cm, its diameter varies from 8 to 15 mm, it is about as thick walled as the human appendix (averaging 15 mm in 13 cases), but the muscularis is much less prominent (averaging about 20 microns in 13 cases), the remainder of the wall being composed of abundant lymphoid tissue and mucosa. The microscopic appearance is shown in figure 2, there are large lymphoid villi covered with epithelium, and between these and extending over them are masses of glandular and epithelial tissue on narrow pedicles. The blood supply comes from the superior mesenteric vessels, a part passes down near the cecal appendage in the mesentery, and the rest comes across the mesentery in a dozen vessels from the ileum.

The cecal appendage of the rabbit therefore differs from the vermiform process of man in having a larger lumen without possibility of spontaneous obstruction, a thinner muscularis and a different configuration of the mucosa and lymphoid tissue. Certain differences in cellular reaction to inflammation have been discussed in a report on cytologic responses.³

PROCEDURES

Anesthesia was routinely induced by pentobarbital sodium given intravenously, except in a few short procedures in which ether was used. Aseptic surgical procedure was, of course, used throughout. A doubled suture of commercial no. 30 linen was placed loosely around the base of the appendage 1 to 2 cm distal to its junction with the cecum, being passed between the organ and the longitudinal vessels in order to spare the blood supply. Two fine silk purse strings were laid, one 5 mm from the tip of the appendage and the second 5 mm behind the first. The tip was punctured for insertion of a glass cannula, which was fastened with the distal purse string, the second being used for inversion of the intervening 0.5 cm of appendage over the cannula, a procedure found necessary to prevent leakage. The contents of the appendage were washed into the cecum with 5 to 25 cc of fluid, usually 0.9 per cent solution of sodium chloride, and the base was obstructed by ligation of the previously placed ties. The wound was closed, the cannula being allowed to emerge at one end. In prolonged experiments anesthesia was usually maintained by subcutaneous injection of pentobarbital sodium or amytal sodium, in many cases the anesthetic was continuously administered together with the daily fluid and sodium chloride requirement, by an electrically driven syringe. In certain cases simple ligation was performed. Variations from these procedures will be detailed with the results.

MICROSCOPIC CLASSIFICATION OF LESIONS PRODUCED

The microscopic changes associated with experimental obstruction of the rabbit cecal appendage have been described elsewhere.³

RESULTS

I *Proof of the Secretory Capacity of the Rabbit Cecal Appendage*—When the obstructed, incannulated rabbit appendages were connected to recording manometers, there was uniformly present a rapid rise in intraluminal pressure. This rise was of course, more rapid with the

3 Buirge, R. E., Dennis, C., Varco, R. L., and Wangenstein, O. H. The Histologic Picture of Experimental Appendiceal Obstruction (Rabbit and Man), Arch. Path., to be published.

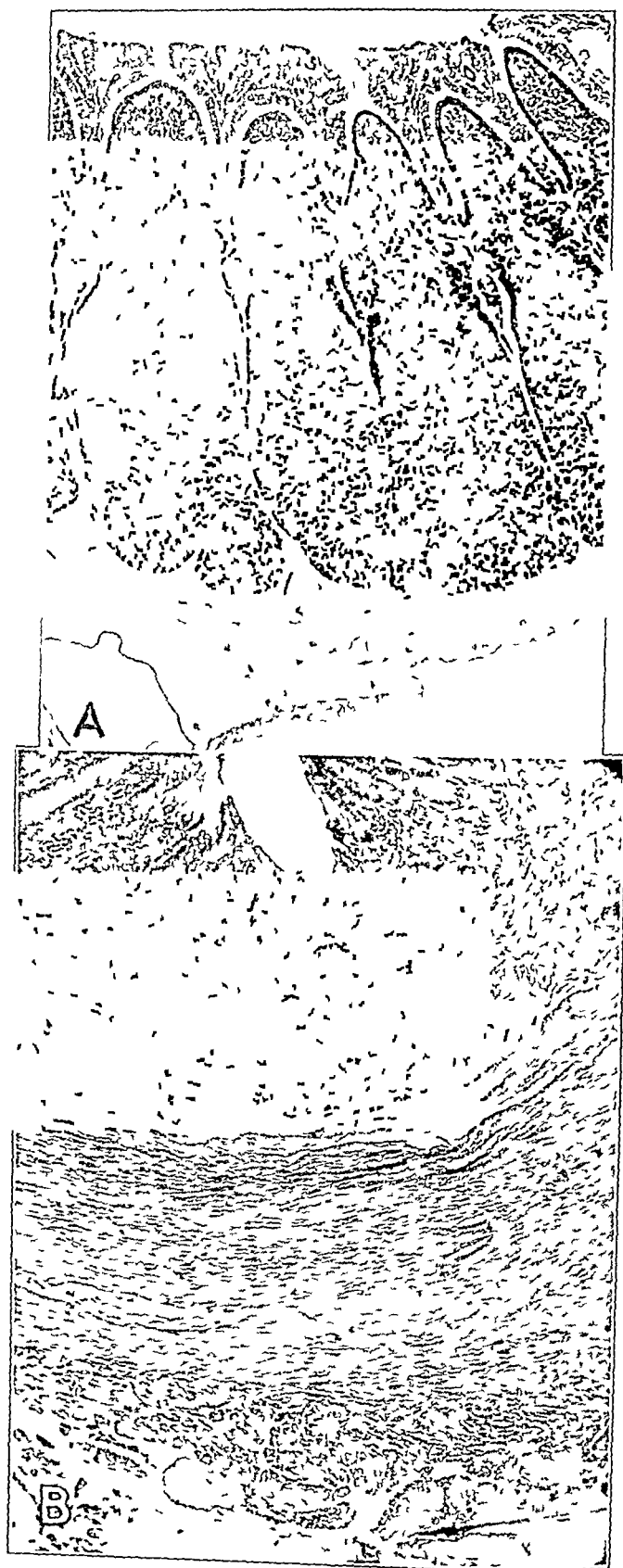


Fig 2—*A*, photomicrograph of the normal cecal appendage of a rabbit ($\times 50$). The appendage is about as thick walled as the human appendix (15 mm), but the muscularis is much less prominent (20 microns), the remainder of the wall being composed of abundant lymphoid tissue and mucosa. There are large lymphoid villi covered with epithelium and, between these and extending over them, masses of glandular and epithelial tissue on narrow pedicles. *B*, photomicrograph of a normal human appendix ($\times 60$). The muscularis is much more prominent than

use of a small volume manometer (requiring ejection of 1 cc of fluid from the appendage to elevate the reading 100 cm of water) than with the use of a large volume instrument (requiring ejection of 20 cc of fluid by the appendage for the same rise in pressure [fig 3]).

When apparatus was prepared to permit maintenance of a constant pressure head against any secretory activity which the appendage might exhibit, the fluid was poured out in each of 26 experiments performed. The rate of ejection of fluid by the appendage varied from 20 to 80 cc daily, varying primarily with the passage of time (fig 4). In 10 cases of ligation and incannulation, rubber condoms were attached to the

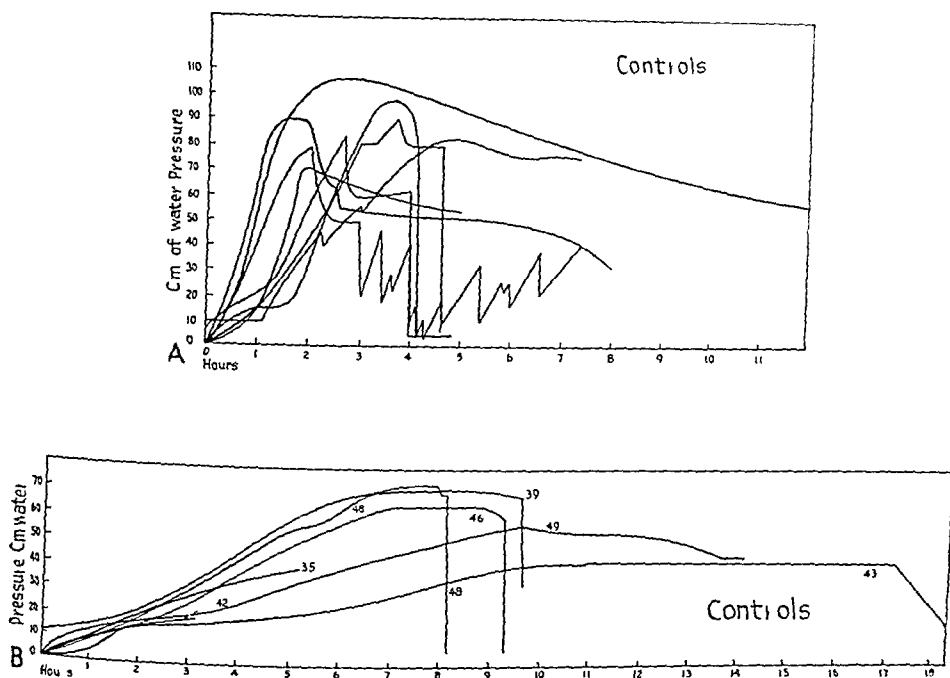


Fig 3—A, rate of rise in pressure in the obstructed, incannulated rabbit cecal appendage (Apparatus 1 cc = 100 cm of water) B, rate of rise in pressure in the obstructed, incannulated rabbit cecal appendage (Apparatus 20 cc = 100 cm of water)

cannulas and dropped into the abdomens, the rabbits being allowed to recover. Fluid uniformly accumulated in the condoms, occasionally in sufficient quantity to cause evident abdominal distention.

II *Effects of Increased Intraluminal Tension*—Pathologic changes in the wall of the rabbit appendage occur as a result of the rise in intraluminal pressure following ligation near the base. In all cases of complete obstruction in which the process was not artificially interrupted either seepage or gross rupture occurred. As has been described for the human appendix,⁴ seepage often occurs in sufficient quantity

⁴ Dennis, C. and Wangenstein, O. H. Unpublished data.

to permit the escape of fluid rapidly enough for a fall in intraluminal pressure to occur. Examples of both seepage (gradual fall in pressure) and rupture (abrupt fall in pressure) are shown in figure 3. Occasionally peritoneal sealing occurred sufficiently fast to permit rise of pressure after rupture, and in rare instances this happened many times in the same preparation (fig. 3A).

The amount of stretching of the appendical wall was judged by change in luminal volume, which was determined at either 10 or 20 cm

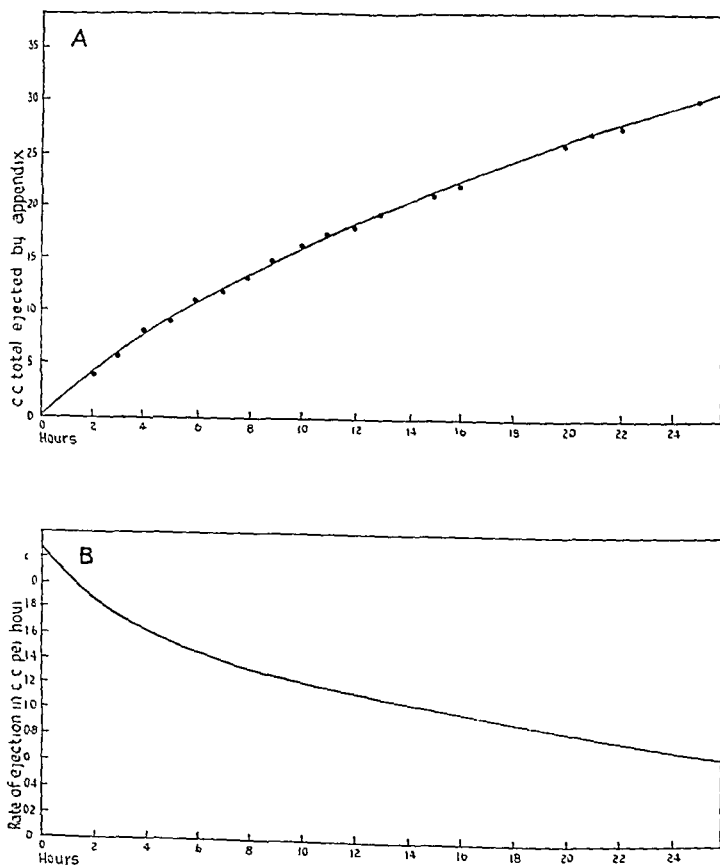


Fig. 4—Changes in rate of ejection of fluid against 5 cm. of water pressure by an incannulated, obstructed rabbit cecal appendage. A, absolute amount ejected, B, rate of ejection in cubic centimeters per hour.

of water pressure by attaching the cannula in the appendage to a T tube, one arm of which led to a volume-calibrated manometer and the other to a calibrated syringe. Marked stretching of the wall of the appendage occurred as the pressure rose after obstruction, the amount of increase in luminal volume depending more on the duration than on the amount of the increase in pressure (table 1).

Histologic changes characteristic of acute appendicitis were regularly encountered when sufficient time had been allowed to elapse after ligation. That these changes were not the result of faulty technic is demonstrated by a series in which the appendage was ligated 2 cm distal to the true base and sections were taken at the conclusion of the experiment from the segment proximal to the tie as well as distally (table 2). In 13 experiments significant acute appendicitis was encountered in all but 1 specimen distal to the tie (the one exception being in a four-hour experiment, near the lower time limit for histologic changes) while 12 of the 13 animals either were normal or presented the inconsequential

TABLE 1—*Luminal Volume Changes During Recordings of Rabbit Cecal Appendages*

Rabbit	Duration of Experiment, Hours	Maximum Pressure, Cm of Water	Initial Volume, Cc	Final Volume, Cc
116	9	35 plus	6.2	25
125	8	82	0.9	4
126	4	70	3.8	6
127	8	41 plus	7.0	27
136	9	85	2.5	4.2
137	29	46	1.6	8.1
142	6	95	0.8	3
145	20	40	1.1	25
146	26	23 (constant)	Not done	9
149	46	20 (constant)	Not done	35 (approx.)
150	29	20 (constant)	Not done	16
152	21	6 (constant)	2.6	6.4
157	24	20 (constant)	Not done	17
160	70	20 (constant)	Not done	20
Mean	—	—	3.0	13.8

The small initial volumes recorded in this table are due largely to the rigidity implied by the presence of the cannula and inversion over it, for when 4 normal appendages were removed and cannulated at the base without inversion the volumes at 10 cm of water pressure averaged 5.3 cc.

*Determined at a pressure of 10 cm of water.

picture of serosal appendicitis³ proximally. The specimen which showed acute inflammation proximally showed gangrene distally and had been allowed to wait eight days after ligation.

In order to determine the effect of prolonged maintenance of pressure in the living appendage on the pressure required to rupture the organ, comparisons were made between the rupturing pressures with the "rapidly rising small volume apparatus," with the "slowly rising large volume apparatus" (both of which have been described) and finally by acutely distending normal appendages. In this manner it was found that rapid deterioration of the wall occurred under the influence of increased intraluminal pressure, so that the bursting pressure was cut to one half in less than twelve hours (table 3). This conclusion is

in agreement with that of Sperling and Wangenstein⁵ as to the dog's intestine in simple obstruction

III *Proof that Pathologic Changes Are Not Due to Ligation Proper Rather than to Increased Intraluminal Pressure*—That the

TABLE 2—*Control Data on Rabbit Appendicitis*

Rabbit	Duration of Obstruction	Microscopic Diagnosis of Condition Distal to Ligature*	Microscopic Diagnosis of Condition Proximal to Ligature*
191	4 hours	Serosal appendicitis, grade 1	Serosal appendicitis, grade 1
192	4 hours	Mucosal appendicitis, group A, grade 2	Normal
176	4 hours	Diffuse appendicitis, grade 1	Normal
183	4½ hours	Mucosal appendicitis, group A, grade 1	Serosal appendicitis, grade 1
178	9¼ hours	Mucosal appendicitis, group A, grade 3	Serosal appendicitis, grade 1
175	10 hours	Diffuse appendicitis, grade 2 (gangrenous)	Serosal appendicitis, grade 2
197	10¾ hours	Mucosal appendicitis, group B, grade 4	Normal
177	20 hours	Diffuse appendicitis, grade 1	Serosal appendicitis, grade 1
184	22 hours	Mucosal appendicitis, group B, grade 4	Serosal appendicitis, grade 2
187	24 hours	Mucosal appendicitis, group B, grade 4 (gangrenous)	Normal
190	2 days	Diffuse appendicitis, grade 2	Serosal appendicitis, grade 2
194	5 days	Healing appendicitis, granulocytes	Serosal appendicitis, grade 1
195	8 days	Healing appendicitis, granulocytes (gangrenous)	Mucosal appendicitis group A, grade 1, healing

* The ligature was placed 2 cm distal to the true base

TABLE 3—*Effect of Prolonged Maintenance of Elevated Intraluminal Pressure on Bursting Pressures of Rabbit Cecal Appendages*

Normal Appendage Acutely Distended Pressure, Cm of Water	With Small Volume Apparatus		With Large Volume Apparatus	
	Time Hours	Pressure, Cm of Water	Time, Hours	Pressure, Cm of Water
150	4	85	8¼	72
140	4 1	90	9½	71
120	2	79	9½	66
140	2	86	13¾	57
			17¼	43
Mean 137½	3 03	85	11½	61 3

pathologic changes observed were not due to ligation of the appendical base rather than to the secondary rise in pressure is evidenced by 2 experiments in which the base was ligated and incannulated in the

⁵ Sperling, L, and Wangenstein, O H Influence of Obstruction of the Bowel on Its Strength (Bursting Strength), *Proc Soc Exper Biol & Med* 32 1183, 1935

usual fashion but in which the pressure was not allowed to rise above 5 cm in the one case and 6 cm in the other. After sixty-seven and twenty-one hours, respectively, the specimens showed inconsequential³

TABLE 4—*Fate of Rabbit's Cecal Appendage Subjected to Simple Ligation Obstruction at the Base*

Duration	Rabbit	Abdominal Mass Palpable	Distended	Serosal Tear	Rupture	Gangrene	Adhesions	Peritonitis (General G Local L)	Serosal Appendicitis	Mucosal Appendicitis (Group A)	Mucosal Appendicitis (Group B)	Diffuse Appendicitis	Healing Appendicitis
1 hour	180	0	0	0	0	0	0	0					
3 hours	182	0	0	0	+	0	+	L					
4 hours	191	0	++	0	0	0	0	0	1				
4 hours	176	0	+	0	0	0	0	0				1	
	WaWi												
5 hours	BD1	0	++	0	0	0	0	0				1	
5 hours	BD2	0	+++	0	0	0	0	0					
6 hours	BD19	0	+	0	0	0	0	0		2		3	
6 hours	BD20	0	+	+	0	0	0	0				3	
7½ hours	BD10	0	0	+	+	+	0	L					
7½ hours	BD11	0	+	0	0	0	0	0		2			
8 hours	188	+	0	—	+	0	+	G					
9 hours	178	—	0	—	+	+	+	L		3			
	Wi												
10½ hours	175	—	++	0	0	+	+	0				2	
	WaWi												
11½ hours	165	—	0	—	+	+	+	G				1	
	Wi												
19 hours	177	—	0	—	+	0	+	0				1	
	Wi												
24 hours	187	+	?	—	+	0	++	0			4		
30 hours	55	?	+	—	+	+	+	G			4		
	D												
48 hours	190	+	?	—	+	0	++	G				2	
4 days	180	0	0	—	+	+	++	0				2	
	D												
9 days	195	?	0	—	+	0	+	G					+
	D												
9 days	44	+	0	—	+	+	++	G					+
	Wa												
9 days	45	?	+	—	+	0	+	G					
	Wa												
3 months	193	+	*			+++	++++	G++					
	D												

* This appendix had become necrotic beyond recognition and was lost in a mass of adhesions stronger than the remaining bowel. Numerous small pockets of pus and caseous material were to be found on cutting into this mass.

The figures below the group classifications of the type of appendicitis indicate the grade.

'Wa' indicates that the lumen of the appendix was washed through a cecostomy prior to obstruction.

'Wi' indicates that a window was inserted into the abdominal wall for observation of the course of events. 'D' indicates that the animal died of the disease in all other cases the appendices were obtained surgically or by killing the rabbit.

† Healing appendicitis with polymorphonuclears.

serosal appendicitis (type I) in the one case and no inflammation in the other (although there was edema of the mucosal pedicles).

IV *Effect of Simple Ligation of the Rabbit Cecal Appendage*—
In order to learn the course of events consequent to simple obstruction of the rabbit cecal appendage, ligation near the base was performed in a series of 22 animals, and reexamination was made at intervals thereafter varying from one hour to three months (table 4). Masses due to

dense and extensive adhesions were palpable through the intact abdominal wall in a large number of experiments in which eight hours or more had been allowed to pass after ligation, in this group perforation and peritonitis were the rule. With the lapse of time the appendage fills tensely, and areas on the surface become blanched and ischemic, occasionally hemorrhagic and finally often gangrenous, at about eight hours rupture usually occurs, releasing tension and culminating in local and then in general peritonitis and extensive formation of adhesions. The microscopic picture is at first only that of serositis but is later more involved, with granulocytes diffusely spread (diffuse appendicitis) or chiefly collected in an infectious process in the mucosa (mucosal appendicitis, group A) or with primarily an infarction of much of the mucosa and only secondary inflammation (mucosal appendicitis, group B). These changes were in general increasingly severe with the passage of time up to forty-eight hours, but at nine days healing processes were well established. Unless killed early, the animals almost invariably died of complications of the disease.

In order to check the relation of changes in pressure to the rate of stretch of the appendical wall, 4 rabbits were subjected to simple ligation, and glass windows were placed in the abdominal wounds, the air in the abdomens being displaced by isotonic sodium chloride solution. The changes in diameter of the appendages are illustrated in figure 5. The dotted curve is a theoretic one, disregarding the thickness of the walls and based on the suppositions that the increase in luminal volume is constant in rate and that an hour was required to fill the appendage initially. The closeness of the curves representing experiments in which rupture did not occur early to the theoretic curve justifies the supposition that the rate of increase in volume is roughly constant until rupture.

During the experiments with the abdominal window it was also possible to observe changes in the appendical wall with advancing distention. The appendix regularly was tense within an hour or two, and shortly the whole organ became somewhat blanched, occasionally with slight movements and obliteration of first the smaller and later the larger vessels. Peristalsis in the ileum became decreased, irregular or (often) reversed in direction at two to three hours, and these changes persisted, though activity in general diminished markedly. At three to four hours some of the lymph follicles seen through the appendical wall commenced to show petechial hemorrhages and others to become acutely blanched, one or two at first and then more, till at seven or eight hours nearly all were blanched, many with petechiae about them. At six to eight hours larger areas, 5 to 20 mm across, became obviously devoid of blood supply, and in other areas larger hemorrhages appeared. Finally the ischemic areas broke down and became necrotic, and rupture

ensued. It seems likely, therefore, that this was a process of ischemic necrosis.

V *Proof of the Absorptive Function of the Cecum*—The question arose whether the cecum as well as the appendage pours fluid into the lumen. This was settled with a single animal by ligation of the cecum 5 cm distal to the ileocecal valve and incannulation just distal to the tie, a blind segment being made of the cecum and appendix together

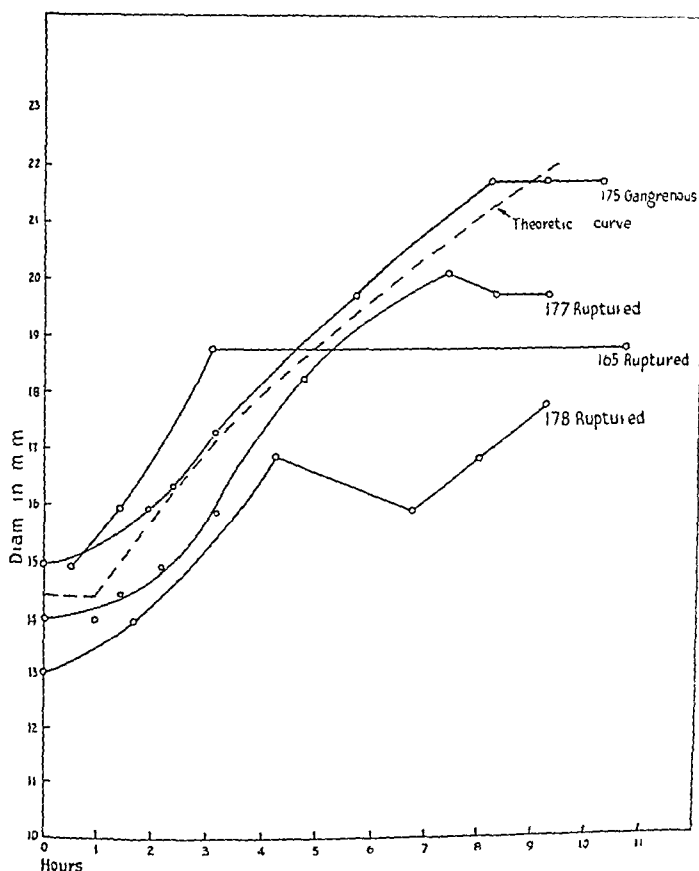


Fig 5—Changes in diameter of rabbit cecal appendages after ligation obstruction at the base, measured through a glass window in the abdominal wall. The dotted line indicates the theoretic curve obtained, assuming the rate of volume increase to be constant. The terms "ruptured" and "gangrenous" refer to the findings on laparotomy at the end of the experiment.

Over 50 cc of fluid was absorbed in five hours. The ligature was removed and the cecostomy closed, the animal being allowed to recover. Four days later the appendage was ligated at the base and incannulated routinely, the pressure rose to 95 cm in four hours. It is therefore concluded that, although the appendage secretes large amounts of fluid, the cecum absorbs.

VI *Lack of Effect of Washing the Lumen*—As it was routine to wash the lumen in order to remove any possible fecal matter which might plug the cannula or the tubing, a series of 7 experiments without preliminary washing was performed, parallel with a second series (of 14) in which each lumen was washed initially with 10 to 20 cc of 0.9 per cent sodium chloride solution. When experiments of similar duration and with similar pressure were compared, no clear relation was found between cytologic reaction and preliminary washing.

VII *Influence of Certain Drugs on the Secretion Rate of the Rabbit Cecal Appendage*—On the assumption that rate of rise in pressure is a measure of the rate of secretion of fluid, the effects of a number of drugs were examined with the aid of the recording manometer. In some cases comparisons were possible with the findings at laparotomy at various intervals after simple ligation and with various time relations between ligation and administration of the drug. In addition, the volume of fluid collected in an intraperitoneal balloon (see the foregoing sections) connected to the obstructed appendage in a given interval after operation and administration of the drug offered a measure of the effect of that drug.

Pitressin, pilocarpine, atropine and epinephrine were studied only in single instances with the recording manometer, and no distinct effect was encountered except for slowing of secretion by 0.5 cc of epinephrine hydrochloride (1:1,000) given subcutaneously, at the conclusion of this experiment, thirty hours later, the entire mucosa was necrotic. Topical applications of 1 per cent pilocarpine hydrochloride resulted in contraction of the appendical musculature. The effect of doses of magnesium sulfate varying from 0.5 to 2 Gm, given by stomach tube, was explored with the aid of the kymograph in 4 cases, with no conclusive evidence of effect on secretion rate.

Fifteen per cent sodium chloride solution in doses of 0.33 Gm of salt per kilogram of body weight was injected intravenously because of marked strengthening of peristalsis which this medication produces. On the basis of 1 of a total of 3 experiments, it was suggested in the preliminary report^{1a} that an accelerating effect might be present. Further kymographic studies, however, show no such effect (fig. 6) as compared to a series of control experiments (fig. 3A), they suggest, on the other hand, a delay of commencement of rise in pressure for one and one-half to two hours. Thirteen rabbits were subjected to simple ligation of the cecal appendage, and the hypertonic saline solution was injected at various times from an hour before ligation to four hours after, the animals being killed at intervals from five to ten hours after operation, the findings were closely parallel to those of control experiments (table 5) except

that serosal tears occurred earlier in the animals treated by injection than in the controls. Experiments with collection of fluid in an intraperitoneal balloon showed no effect from intravenous hypertonic saline solution (table 6)

It was considered that the decrease in time till the serosa tore after intravenous injection of 15 per cent sodium chloride might be due to secretion of some of the excess chloride into the appendix and the passage of fluid with it, however, chloride determinations were made on the fluid from the five, six and seven hour experiments, and the mean values were not altered (499 mg per hundred cubic centimeters for the controls and 493 mg for the experimental fluids). Three animals given 25 cc of 0.9 per cent sodium chloride each at the time of ligation showed serosal tears at five and seven hours and rupture at six hours, in these the mean chloride content was 574 mg per hundred cubic centimeters, significantly higher than that of the controls (probable error 37 mg

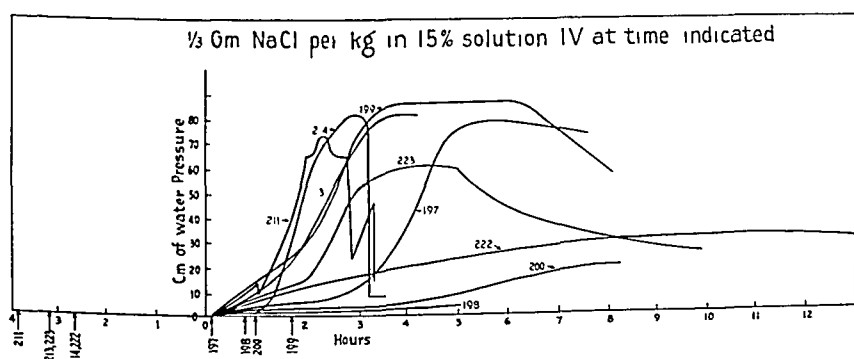


Fig 6—Effect of intravenous hypertonic sodium chloride solution on the rate of rise in pressure in the obstructed, cannulated rabbit cecal appendage (Apparatus 1 cc = 100 cm of water) The arrows indicate the time of injection (see figure 3A)

per hundred cubic centimeters for experiments with saline solution, and 28.3 mg per hundred cubic centimeters for controls)

Castor oil in doses of 20 to 30 cc, given by stomach tube, produced no alteration from the result for controls in 1 kymographic experiment or in 4 experiments with simple ligation in which the drug was administered at four and one-half hours and the animals were killed at ten hours, but 5 experiments with the intraperitoneal balloon technic showed that significantly less fluid had been ejected in six to seven hours than in the control experiments (table 6)

In 2 kymographic experiments, croton oil in doses up to 0.2 cc resulted in an elevation of the rate of secretion slightly above that of any of 8 controls, but 9 animals given 0.1 cc into the jejunum and subjected to simple ligation presented findings identical with those for the

controls at five, six and seven hours, 4 animals given 0.2 cc four and one-half hours after ligation presented findings identical with those of controls at ten hours, and, finally, 4 animals given 0.2 cc at the time of insertion of the balloon and ligation showed ejection of fluid at essentially the same rate as 5 controls (table 6)

TABLE 5—*Effect of Intravenous Injection of Five Cubic Centimeters of Fifteen per Cent Sodium Chloride Solution on Events After Ligation Obstruction of the Cecal Appendage of the Rabbit*

Duration Hours	Injection 1 Hr Before Ligation	Injection at Time of Ligation	Injection 1 Hr After Ligation	Injection 4½ Hr After Ligation	Controls	
					A	B
5	Serosal tear	Serosal tear	Gangrene, rupture		Tense	Very tense
6	Serosal tear	Tense and hemorrhagic tear	Serosal tear		Tense, but no rupture	Tense, grossly acute appendicitis
7	Serosal tear	Serosal tear	Rupture		Serosal tear, rupture, gan- grene	Tense
10¼				Acute ap- pendicitis, rupture	Acute appendicitis, rupture	
10¼				Acute ap- pendicitis rupture	Pale, tense	
10¼				Acute ap- pendicitis, rupture	Acute appendicitis, rupture	
10¼				Acute ap- pendicitis, rupture	Acute appendicitis, rupture	

TABLE 6—*Effect of Hypertonic Intravenous Saline Solution, Croton Oil and Castor Oil on the Rate of Fluid Ejection by the Ligated Rabbit Cecal Appendage into an Intra-Abdominal Balloon*

	Number of Rabbits	Mean Time Till Rabbit Was Killed, Hours	Mean Volume Collected, Cc	Minimum Volume Collected, Cc	Maximum Volume Collected, Cc
Controls					
Given 5 cc of 15% sodium chloride intravenously	5	6.3	22.4	17	27
Given 0.2 cc of croton oil	5	7.3	24	15	46
Given 0.2 cc of castor oil	4	8.1	25	17	32
	5	6.6	15.8	5	24

VIII *Lack of Effect of Age of Animal on Secretion Rate*—Four old animals were obtained with considerable difficulty, and the rate of rise in pressure was tested with the apparatus requiring ejection of 1 cc of fluid for the recording of each 100 cm of rise in water pressure. Two animals 2 years old and 1 animal 3 years old fell in the high normal range of the controls shown in figure 3A (the controls were animals less than 1 year old, the life span of domestic rabbits is about eight years). In 1 animal, 5 years old, the rate of rise in pressure was

12 cc per hour, at the lower limit for the controls, but technical difficulties cast doubt on this finding. Microscopic examination of these 4 appendages showed no significant difference in amount of lymphoid tissue from those of younger animals.

IX Effect of Appendicostomy on Secretory Rate—In 2 animals appendicostomy with delayed (eleventh day) opening of the tip was performed, the fistula thereafter being kept open by cannula. Four days after opening to the outside the appendages were ligated at the base and cannulated at the tip for kymographic recording. In 1 the curve of pressure rise fell in the center of the control range shown in figure 3, 4, in the other it rose to 48 cm in four and one-half hours four days after opening of the tip, and to 63 cm in four and one-half hours seven days after opening of the tip. In both instances it rose more slowly than the slowest of the control group.

TABLE 7—*Effect of Previous Elevations of Pressure on Rate of Pressure Rise in the Obstructed Rabbit Cecal Appendage*

Pressure Rise No	Time Required for Rise from 7 to 40 Cm of Water	Volume Removed from Appendage in Fall from 40 to 7 Cm, Cc
1	1 hr 50 min	5
2	1 hr 52 min	5½
3	2 hr 18 min	5½
4	5 hr 36 min	5
5	Falled	

The final rise was slow, reaching 24 cm in 4 hours and then falling slowly during 6 more hours. The appendage was found somewhat stretched and also ruptured.

In 2 rabbits appendicostomies were made at the conclusion of recording experiments, the proximal ends remaining obstructed. In both the drainage was watery for two to three weeks and mucoid for another two weeks, after which time the stomas closed completely. With closure, the animals became ill and inactive, one dying two months, and the other two and one-half months, after appendicostomy. At autopsy there was abundant purulent and caseous exudate in the peritoneal cavities of both of these animals, in 1 the appendix could not be found, and in the other it was a necrotic, foul mass. It is evident, therefore, that, although the amount of secretion may decrease somewhat, enough remains to invoke a fatal series of events on closure of the stoma.

X Effect of Previous Elevations of Pressure on Rate of Pressure Rise in the Obstructed Rabbit Cecal Appendage—Experiments were done on 2 animals to determine the effect of a previous rise in pressure from 7 to 40 cm of water on the subsequent rises over the same range. For this purpose a siphonage apparatus was arranged which lowered the pressure to 7 cm automatically after it had reached 40 and measured the volume of fluid removed from the appendage in so doing.

Both experiments showed a slow rise after the second siphonage. One showed at the end that marked stretching of the wall had occurred, and the other showed almost no stretch. The first of these is shown in table 7. Diffuse appendicitis was encountered in each case.

XI Effect of Prolonged Pressures at Fixed Levels on Rate of Fluid Production by the Obstructed, Incannulated Rabbit Cecal Appendage—It seemed at least equally important to determine the effect of fixed pressures at various levels on the rate of secretion of fluid and incidentally to determine the height of pressure required to incite an inflammatory reaction. For this purpose 5 experiments were

TABLE 8—*Effect of Prolonged Pressures at Fixed Levels on Rate of Fluid Production by the Obstructed, Incannulated Rabbit Cecal Appendage*

Rabbit	Pressure, Cm of Water	Decrease in Secretion Rate with Lapse of Time	Duration, Hours	Microscopic Diagnosis
159	5	Yes	67	Serosal appendicitis, grade 1
152	6	Yes	21	Normal*
S20 1	10	Yes	9	Mucosal appendicitis, B1
S20 4	10	Yes	29	Mucosal appendicitis, B1
S20 6	10	Yes	74	Postmortem autolysis
S20 3	10	Yes	23½	Mucosal appendicitis, B3
S20 2	10	Yes	63	Mucosal appendicitis, B4
S20 5	10	Yes	72	Diffuse appendicitis, gr 1
124	20	No	23	Mucosal appendicitis, B1
149	20	No	46	Mucosal appendicitis, B4 (gangrene, rupture)
160	20	Yes	53½	Mucosal appendicitis, B4
146	23	Yes	25	No section
163	40	Yes	12	Mucosal appendicitis, B1
164	40	Yes	23	Mucosal appendicitis, B4
12 rabbits	40	All Yes	Average 15.2	All grossly acute

* Although the appendage in this experiment showed no changes which fit our classification of appendicitis in the rabbit, there was edema of the mucosal pedicles extending up between the lymphoid villi.

performed with an appropriate kymographic recording apparatus, and 21 additional experiments, planned primarily for collection of fluid at divers pressures (to be reported), provided further data on changes in rate of secretion. The volume measured in such experiments represents the rate of ejection rather than the rate of secretion, the difference being the change in luminal volume due to stretching of the appendical wall. The findings in 1 of the experiments with kymographic recording are presented in figure 4, in this instance the increase in luminal volume was less than 5 cc (insignificant in comparison to the changes in rate of ejection), and the rate of net transfer of fluid into the appendical lumen therefore decreased with the lapse of time.

The 26 experiments offering evidence in this connection are presented in table 8, all but 2 of this group showed a decrease in rate of secretion with the passage of time. Ten centimeters of sustained intra-

luminal pressure resulted in 4 of 5 cases primarily in infarction of the mucosa, 6 cm of water pressure led to edema and some disorganization of the mucosa but no change severe enough to fall into our classification, and 5 cm caused no change. In 12 of the 13 microscopically diagnosed lesions the changes consisted of infarction of the mucosa (mucosal appendicitis, group B) with or without secondary granulocytic invasion.

XII Effect of Catharsis at the Time of Rupture on the Course of the Disease—In an attempt to test the factor of interference with adhesion formation 4 rabbits were given 0.2 cc of croton oil on the tongue, 4 were given 30 cc of castor oil by gavage and 4 were given 10 cc of 15 per cent sodium chloride intravenously at the time of simple ligation.

TABLE 9—Effects of Hypertonic Intravenous Saline Solution, Croton Oil and Castor Oil on Survival of Rabbits After Ligation of the Cecal Appendage

	Rabbit	Survival Period	Gross Findings
Controls	301	14 days	Rupture abscess
	304	2 days	Rupture acute inflammation
	306	2 days	Acute appendicitis, multiple ruptures
Given 0.2 cc of croton oil	310	7 days	Rupture abscess
	302	2 days	Rupture, acute appendicitis
	307	17 days	Rupture abscess
	311	11 days	Rupture abscess
	315	8 hours	Rupture, acute appendicitis
Given 30 cc of castor oil	303	10 days	Rupture, abscess
	308	3 days	Rupture abscess
	312	59 days	Normal appendix
	316	6 hours	Rupture, acute appendicitis
	305	Killed at 129 days	Mucocele
Given 10 cc of 15% NaCl intravenously	309	11 days	Rupture abscess
	313	2 days	Rupture acute appendicitis
	317	67 days	Mucocele

of the true base of the cecal appendage. These medications caused increased numbers of stools but no diarrhea. The average survival period of 4 control animals was six and one-fourth days, the average survival period of those given croton oil was seven and one-half days, that of those given castor oil was eighteen days, and that of 3 of those given hypertonic saline solution was twenty-six and two-thirds days, the fourth being killed at one hundred and twenty-nine days. Of particular interest is the observation that, although the average periods of survival were longer after croton oil or castor oil than in the control group, 1 rabbit of each of these groups given a cathartic survived eight hours or less, a more rapid death than was ever seen in control animals (table 9).

XIII Studies Involving Traumatization of the Mucosa—Wells⁶ has reported a series of experiments concerned with appendicitis in the

⁶ Wells, A. Q. Experimental Lesions of the Rabbit's Appendix, *Brit J Surg* 24 96, 1937.

rabbit and concluded that obstruction by ligation occasionally results in mucocele formation with masses palpable through the abdominal wall, but "that the only experimental procedure which consistently produced acute appendicitis was obstruction to the lumen of the appendix combined with damage to the mucous membrane" He accomplished that traumatization either by crushing the appendage between the fingers⁷ or by transfixing one wall with a needle and scratching the mucosa of the opposite wall In view of this wide difference of opinion, it seemed worth while to repeat his procedure, also with some variations

In 2 appendages the walls were rubbed and crushed between the fingers, the wounds were closed and the animals were allowed to awaken The specimens, removed seven and one-half hours later, showed mucosal appendicitis, group A, grade 3, and diffuse appendicitis, grade 2, respectively

In order to evaluate the effect of traumatizing the mucosa by scratching with a needle in combination with ligation, a series of 8 rabbits was so treated beside a series of 8 controls, 6 of each being opened at intervals from one hour to two days and 3 being allowed to live till killed by the disease (including 1 opened aseptically at one hour) Although 4 of the control series presented masses palpable through the abdominal wall after eight hours, no masses were to be found in the experimental series Rupture or leakage through the site of the needle holes occurred in 2 instances, in animals dying at twelve and thirty-eight days, respectively The microscopic observations were still within normal limits at four hours in the controls, but the traumatized four-hour appendage and all subsequent ones showed advanced changes, with diffuse involvement at the needle holes The only mucocele in either series occurred in 1 of the animals treated by the Wells technic which died at thirty-eight days, but in the only control rabbit to live for this length of time the appendix could not be found, and caseous exudate abounded in the peritoneal cavity

In order to be certain that no possible point of difference was being overlooked, the changes in pressure also were investigated by Wells's scratching technic Five animals were subjected to ligation, scratching of the mucosa, incannulation and pressure recording, in addition, 5 animals were similarly treated except that the mucosa was curetted with a fine bone curet instead of being scratched The records were within the limits of variability for the controls shown in figure 3 except for 1 of the curetting experiments in which most of the mucosa was removed, only in this case was the rate of rise in pressure slow and the ultimate pressure below that recorded for the controls

7 Personal communication to the authors

With regard to mucocoele formation, we have been able to produce this condition with simple ligation only if the tie is loosely placed, with this technic mucocoele has been produced on each of 5 trials.

For these reasons we find it impossible to corroborate Wells in his opinion that operative trauma to the mucosa as well as ligation obstruction of the lumen is necessary to the development of acute appendicitis in the rabbit.

COMMENT

In the preceding pages it has been shown that the cecal appendage of the rabbit secretes fluid in large amounts and is capable of secreting against a pressure of about 100 cm of water. When the base is obstructed, the intraluminal pressure is elevated by this outpouring of fluid, and acute appendicitis develops in four to six hours with rupture in eight, the process going on to peritonitis, abscess formation, widespread adhesions and ultimately death of the animal. It has been shown, furthermore, that this process is solely the result of increased pressure, for the same technic without tightening of the obstructing ligature³ or the same technic with escape of the fluid at 5 cm of pressure through a cannula placed at the tip did not result in any of these changes but rather in simple low grade serositis from handling the peritoneal coat. The demonstration of Fischer and Kaiserling⁸ that the lymphatics from the rabbit cecal appendage run chiefly across the mesentery makes it unlikely that lymphatic obstruction is a factor.

The production of diffuse polymorphonuclear invasion of the appendical wall, with changes fitting into the classification of appendical lesions which can be produced by obstruction alone has been shown to be achievable by direct trauma, but rupture did not occur in the absence of ligation.

In a group of experiments in which the intraluminal pressure was maintained at a constant level, the predominating lesion was found to be infarction and necrosis of the mucosa with varying degrees of granulocytic infiltration. In 1 experiment, in which the pressure was maintained at 6 cm for twenty-six hours, microscopic examination showed edema and some disruption of the glandular layer without either granulocytic infiltration or actual infarction. Further evidence of the nature of the process is obtained by the use of windows in the abdominal wall, this type of observation demonstrates that the primary change after distention is interference with the blood supply.

In view of the experimental findings which have been discussed in this paper and elsewhere,³ it is seen that the acute appendicitis following ligation at the base of the cecal appendage of the rabbit must develop

⁸ Fischer, E, and Kaiserling, H. Die experimentelle lymphogene allergisch-hyperergische Appendicitis, *Virchows Arch f path Anat* 297 146, 1936

as follows. Increased intraluminal pressure places tension on the appendical wall with consequent pinching off of some of the vessels and resultant formation of foci of ischemic necrosis, offering a weakened area through which rupture may occur and an open field for whatever bacteria happen to be present. Although Bowers⁹ has demonstrated that increased pressure in a sterile hollow viscus can produce granulocytic infiltration, the infiltration in experimental appendicitis in rabbits is probably secondary to bacterial invasion. It has been shown that there is always a greater or smaller number of bacteria in the tissue of the rabbit appendage and that sections from healthy animals often reveal for this reason the presence of a few granulocytes.³ We have seen rupture occur in the rabbit twelve hours after obstruction without sign of granulocytes when very few bacteria could be found on Gram-stained sections.

That secretion in the true sense of the word, rather than transudation secondary to obstruction of venous circulation, is the decisive factor in the appearance of fluid in the lumen is strongly suggested by the occurrence of this transfer against any level of pressure and by the failure of fluid transfer in two dozen other species investigated.²

CONCLUSIONS

1 Simple ligation obstruction of the rabbit cecal appendage results in acute appendicitis presenting all the pathologic manifestations of the human disease.

2 The pressure within the appendical lumen rises after obstruction at the base, and this rise is responsible for the development of appendicitis.

3 The lowest maintained pressure required to initiate the changes characteristic of acute appendicitis is about 10 cm. of water.

4 The rate of fluid secretion is slowed by prolonged pressures at fixed levels.

5 The more advanced the appendicitis, the lower the pressure required to cause rupture of the organ.

6 The effects of various drugs on the rate of secretion of the cecal appendage of the rabbit were tested. None had a marked effect except epinephrine, which stopped the flow.

7 No cathartics studied were found to alter the course of development of acute appendicitis appreciably, but in some instances death was apparently hastened because of inability to localize the infection in the abdomen.

9 Bowers, W. F. The Role of Distention in the Genesis of Acute Inflammation of Hollow Viscera, *Am. J. M. Sc.* **194**: 205, 1937.

PAPILLARY CARCINOMA OF THE PELVIS OF THE KIDNEY

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DETROIT

The general facts and clinical details concerning tumors of the pelvis of the kidney are well known. Though such tumors are rare, there have been several reviews of series of cases, and each year there have been isolated case reports reemphasizing this knowledge.

There were apparently 218 cases reported in 1927, and from then until 1932 there were 30 additional cases (Mackenzie and Ratner¹).

Tumors of the renal pelvis constitute from 1 to 10 per cent of all renal tumors. Five per cent is the average figure usually stated. There are two varieties: the squamous cell tumors, which are the rarer and of which the literature contains only about 60 cases (Higgins²), and the papillary tumors, which comprise three fourths of the total number.

The squamous cell growths are the more malignant. They are usually grade 3 or 4 (Broders' classification), are frequently accompanied by stones and chronic inflammation, spread rapidly through the substance of the kidney and are often hopeless, having already metastasized at the time the diagnosis is established. Nephrectomy is the indicated treatment, but no patient has lived five years free from metastasis, and the average duration of life is six to nine months.

By contrast, the papillary growths are the least malignant of all renal tumors (Hunt,^{3a} Hunt and Hager^{3b}). Gross, sometimes profound hematuria dominates the clinical picture with less emphasis on stones and pyuria. If the growth obstructs the pelvic junction of the ureter,

From Mercy Hall and Woman's Hospital.

1 Mackenzie, D. W., and Ratner, M. Tumors of Renal Pelvis. Review of Literature and Report of Case, *J. Urol.* **28** 405, 1932.

2 Higgins, C. C. Squamous Cell Carcinoma of Kidney Pelvis, *Tr. Am. A. Genito-Urin. Surgeons* **30** 13, 1937, *Arch. Surg.* **38** 224 (Feb.) 1939.

3 (a) Hunt, V. C. Papillary Epithelioma of the Renal Pelvis, *J. Urol.* **18** 225-246, 1927, Method of Metastasis of Papillary Epithelioma of the Renal Pelvis, *S. Clin. North America* **9** 853, 1929. (b) Hunt, V. C., and Hager, B. H. Review of Two Hundred and Seventy-One Cases of Malignant Renal Neoplasms, *ibid.* **9** 149, 1929.

there is pain from hydronephrosis. Distention of the pelvis of the kidney may produce a large renal tumor.

Pathologically the tumors are usually graded 1 or 1 minus and are analogous to papilloma and papillary carcinoma of the bladder, having the same propensity for spread and reappearance in other portions of the genitourinary tract. Accordingly, one finds in the literature the same discussion of pathologic malignancy or benignancy (Werwath⁴), with the same general conclusion that "microscopic benignancy does not insure innocent behavior" and the warning that the original treatment should be radical.

The tumors spread down the submucosa of the ureter to the bladder. Only at a very late stage are the outer coats of the ureter involved (Kimball and Ferris,^{5a} Lower^{5b}).

TREATMENT

In 1919, Judd⁶ did a nephrectomy with partial ureterectomy for a papillary carcinoma of the pelvis of the kidney. The patient was well for nine months, then there was a recurrence of hematuria, and three or four months later the lower portion of the ureter and the adjacent vesical mucosa were resected. There was a cauliflower-like mass $\frac{3}{4}$ inch (1.9 cm) in diameter at the left ureteral meatus. Before Judd's report was published, C. H. Mayo had a patient in whom he fulgurated a papilloma at the ureteral orifice. Three weeks later another attack of severe hematuria called attention to a papilloma in the renal pelvis above. Judd strongly advised resection of the entire ureter with excision of the adjacent portion of the bladder, stating that nothing less radical was sufficient.

Beer⁷ in 1921, Hunt^{3a} in 1927 and 1929, Kimball and Ferris⁵ in 1934, Walters and Braasch⁸ in 1935, Smith⁹ in 1938 and others have emphasized total resection of the ureter together with a portion of the wall of the bladder as the indicated treatment.

4 Werwath, K. Zur Frage der "Gutartigkeit" von Nierenbeckenpapillomen, *Zentralbl. f. Chir.* **64** 2890, 1937.

5 (a) Kimball, F. N., and Ferris, H. W. Papillomatous Tumors of the Renal Pelvis Associated with Similar Tumors in the Ureter and Bladder. Review of Literature and Report of Two Cases, *J. Urol.* **31** 257, 1934. (b) Lower, W. E. Neoplasms of the Renal Pelvis with Especial Reference to Transplantation in the Ureter and Bladder, *Surg., Gynec. & Obst.* **18** 151, 1914.

6 Judd, E. S. Papillary Tumors of the Pelvis of the Kidney, *Journal-Lancet* **39** 247, 1919.

7 Beer, E. Aseptic Nephro-Ureterectomy. Technique and Indications, *J. A. M. A.* **77** 1176 (Oct. 8) 1921.

8 Walters, W., and Braasch, W. F. Nephrectomy and Nephro-Ureterectomy for Malignant Tumors of the Kidney, *Am. J. Surg.* **28** 23, 1935.

9 Smith, G. G. Surgery of Renal Tumors, *J. Urol.* **39** 308, 1938.

Nevertheless, in a large proportion of the cases which have since been reported nephrectomy with or without partial ureterectomy, has been performed. Isolated reports of cases in which nephrectomy was the only treatment still appear (Fritz,¹⁰ Mackenzie¹¹)

Kimball and Ferris⁷ in 1934 were able to collect 74 cases in which the growth was both in the renal pelvis and in the ureter or the bladder. In 40 of these primary nephrectomy only had been done. There was recurrence in 30. Eighty-six per cent of all recurrences appear in the remaining ureteral stump and in the portion of the bladder adjacent to the ureteral orifices.

After primary nephrectomy for papillary carcinoma of the renal pelvis, with partial amputation of a harmless-looking ureter, there may be an immediate change from a benign to a malignant growth (Judd⁶). Ureters which in ureterograms have shown no evidence of tumor transplants may show extensive growths within a few months after nephrectomy (Smith⁹). Secondary ureterectomy may therefore be difficult because of dense adhesions and infiltration. The growth in the pelvis of the kidney may be small, with early and extensive involvement of the ureter and the bladder (Hinman^{11a}). Nevertheless, unless the mass is densely adherent and is hopeless from a surgical or a pathologic point of view, it is always worth doing. In roughly one third of Kimball and Ferris' collected cases secondary ureterectomy was performed with beneficial results.

It is apparently not sufficient to take out the ureter, "funneling out" the intramural portion and closing over the vesical wall at this point, although such a procedure was advocated by Caulk¹² as recently as 1937. The vesical wall for a distance of 1 cm. about the vesical orifice must be excised. The reason is the frequency with which transplants occur at the mouth of the ureter or adjacent to it. Hunt,^{3a} Cabot,¹³ Beer,⁷ Smith⁹ and others have stressed the importance of the intramural portion of the ureter. In one third of Hunt's cases "a tuft of tissue was seen projecting from the ureteral orifice and there was definite extension of the lesion to the area of the bladder immediately adjacent to the ureteral orifice." In Cabot and Allen's¹⁴ series, 19 patients on

10 Fritz, L. H. Papillary Carcinoma of Renal Pelvis, *J. Iowa M. Soc.* **27** 163, 1937.

11 Mackenzie, D. W. Papillary Growths of the Renal Pelvis, *Canad. M. A. J.* **30** 509, 1934.

11a Hinman, F. The Principles and Practice of Urology, Philadelphia, W. B. Saunders Company, 1935, p. 1018.

12 Caulk, J. R. Tumors of the Renal Pelvis and Ureter, *Tr. Am. A. Genito-Urin. Surgeons* **30** 51, 1937.

13 Cabot, in discussion on Caulk¹².

14 Cabot, H., and Allen, R. B. Epithelioma Primary in Renal Pelvis. Report of Forty-Five Cases, *Lancet* **2** 1301, 1933.

whom total resection of the ureter with segmental resection of the adjacent vesical wall was done had 50 per cent longer postoperative life than 26 on whom nephrectomy and partial ureterectomy were performed. Similarly, Smith⁹ noted that in 6 of his 7 cases of ureteral growths there was tumor either in the intramural portion of the ureter or arising from the ureteral meatus.

There have been cases in which the growth repeatedly recurred in the bladder after complete nephrectomy and ureterectomy and the patient was kept alive by repeated fulgurations and segmental resections of the bladder (Patch and Livermore¹⁵).

The following case report illustrates the benign course of papillary carcinoma of the renal pelvis (duration, ten years), the slow progression down the ureter and bladder and the eventual general metastatic spread of this low grade tumor. Also, the patient received treatment for vesical carcinoma in three hospitals without knowledge that the ureter was still in situ and involved in the tumor. At autopsy the renal pouch and the ureteral bed were still free from cancer, although the abdominal cavity was riddled with it, probably owing to extension via the bladder.

The history of this case has been pieced together from the records of eight admissions to seven Detroit hospitals.

REPORT OF CASE

George A., a man aged 46, was admitted to Mercy Hall on Feb 2, 1938.

History—In the summer of 1928, at the age of 38, he had an attack of hematuria. In December there was intermittent abdominal pain. It was not definitely localized but recurred oftenest in the epigastrium, the hypochondrium and the lumbar region, in each instance on the right.

In May 1929 there was hematuria (almost pure blood) accompanied by some distress referable to the bladder.

Examination in the same month revealed cardiac dulness over an area of 25 by 10.5 cm and a blood pressure of 144 systolic and 86 diastolic. The urine gave a 1 plus reaction for albumin and contained 68 white blood cells per high power field and a few red blood cells.

Cystoscopic examination at that time revealed that the vesical urine contained some red blood cells. The first drops from the catheterized right ureter were pure blood, the remainder of the urine was clear.

The dye (phenolsulfonphthalein) did not appear in the right side after fourteen minutes and when it appeared was very pale. On the left side it appeared in three minutes. Three attempts to introduce sodium iodide into the right renal pelvis were only partially successful. Roentgen examination showed a somewhat globular shadow in the right renal area. The diagnosis was tumor of the right kidney.

Nephrectomy was performed on the right side in June. The operation record stated "The usual lumbar incision was made. The right kidney was somewhat

15 Patch, F. S., and Livermore, G., in discussion on Caulk¹²

large but appeared normal except that the pelvis was filled with a soft tumor mass. The kidney and pelvis were removed. The pedicle was ligated with no. 2 catgut."

The gross specimen showed "a papillomatous new growth extending from the pelvis upward toward the cortex. The growth extended outside the pelvis as well as within."

Microscopic examination showed "a papillary epithelial new growth of very uniform, not particularly anaplastic, pattern, on a narrow hyalinized stem. There were also some tubular nephrosis and glomerular congestion in the substance of the kidney."

The pathologic diagnosis was "papilloma of the right kidney, grade 1 malignancy."



Fig 1—Right kidney (surgical specimen, 1929). The renal pelvis is dilated and filled with a papillary growth derived from the pelvic epithelium. The renal parenchyma is atrophic around the growth but is essentially not invaded by it.

The patient was well for two years after this operation, then he began to pass "clumps of tissue, blood and pus" in the urine. Since 1934 there had been moderate bleeding from the bladder. Since 1935 he had become progressively weaker. His legs became tired easily, he had to rest frequently, there was a choking sensation in his chest and there was dizziness when he arose suddenly.

On April 17, 1936, he was admitted to another hospital. There was evidence of cardiovascular disease (mitral murmur transmitted to the axilla and to the apex 14 cm from the midline). Papilloma of the bladder was diagnosed, and five radium needles were inserted into the bladder (for twelve hours) through the urethra.

On May 10 the growth in the bladder was fulgurated at still another hospital (the fourth).

On July 17, 1937, cystoscopic examination showed that the tumor which had been fulgurated two months before had disappeared. However, there was a large, compact tumor in the bladder, to the right of the midline, with three or four pea-sized implants on the wall of the bladder.

On August 26 a cystoscopic procedure was done. A specimen removed was diagnosed as carcinoma of the bladder.

On September 25 a suprapubic cystotomy was done at a fifth hospital. A large pedunculated tumor from the left side of the trigon was fulgurated. The pedicle was severed with the electric knife. The remainder of the pedicle was removed to the submucosa, and that area was coagulated.

There was a steady pain down the left leg, unrelieved by change in position.

On October 1 he was admitted to a sixth hospital. The heart was greatly enlarged, and there were marked evidences of hypertensive disease. Cystoscopic study showed three papillary granulomatous masses on the base of the bladder. These were fulgurated. Roentgen study showed diffuse destruction of bone in the left acetabulum and ilium. He was transferred for palliative high voltage roentgen therapy and was discharged from the hospital (the seventh) on December 19.

On his admission to Mercy Hall (the eighth hospital), on Feb. 21, 1938, there were severe backache and pain down the left leg. There was slight pain also in the suprapubic region. Examination showed the patient to be rather stocky, with marked cardiac enlargement and with other evidences of hypertensive disease and rales in the bases of both lungs. The pain in the back increased, as did the hematuria. On March 8 he became drowsy and irrational, had hiccups and gradually sank into coma. He died on March 10.

Summary of Case—The patient had a low grade papillary carcinoma of the right renal pelvis with onset of symptoms in December 1928, when he was 38 years old.

Nephrectomy with ligation of the pedicle was performed on the right side six months after the onset of symptoms. There was freedom from symptoms for two years, then there was recurrence of the bleeding and appearance of pus in the urine. The patient sought treatment in several institutions. Papillary carcinoma of the bladder was diagnosed cystoscopically and pathologically on three separate occasions during 1936 and 1938, and treatment for carcinoma of the bladder was given on three separate occasions. The patient died on March 10, 1938.

Abstract of Autopsy Report—Gross Findings. The body was extremely emaciated. The scars of ancient "lower midabdominal," McBurney and "right Mayo kidney" incisions were seen. The entire left lower extremity was enlarged owing to edema. There was only slight edema of the right foot.

When the peritoneal cavity was opened there was observed nodular, firm and conglomerate enlargement of the lymph nodes of the right and left iliac chains, much more extensive on the left than on the right. The nodes were white and partially necrotic. They formed a mass which was partly attached to the bladder and prostate and extended along the aorta to the region of the celiac axis. The vena cava, aorta and iliac vessels were compressed. Metastases to pelvic bones were present.

The lungs revealed irregularly increased consistency due to a nodular type of consolidation. On cut surface the nodules were white to light pink, 3 to 0.5 cm in diameter, firm and discrete. Portions of the lungs not so involved were emphysematous.

The heart was enlarged, the transverse diameter being increased to 15 cm. Its weight was 600 Gm.

The esophagus was normal, but on the lesser curvature of the stomach, about 8 cm above the pylorus, there was a superficial ulcer measuring 3 by 5 cm. The remainder of the intestinal tract was normal.

The liver weighed 1,600 Gm. The capsule was generally smooth and glistening, but multiple firm white nodules of varying size were distributed over the surfaces of both lobes. These were from 0.5 to 1.5 cm in diameter. The cut surface had a



Fig 2—Ureters and urinary bladder (postmortem specimen, 1938). Note the papillary growth originating from the mucous membrane of the dilated right ureter, the smooth but dilated left ureter and the papillary growth in the bladder (especially in the region of the trigon and at the top of the fundus). The right renal fossa and the tissues around the ureter revealed no recurrence.

nutmeg appearance and exhibited multiple nodules similar to those on the surface of the liver.

The right kidney was absent. There was no evidence of recurrence in the right renal fossa or in the tissue surrounding the right ureter.

The right ureter was present from its origin in the right renal fossa. It was dilated to 1.5 cm in diameter and was firm and white. The wall was thickened. When the ureter was opened, milky, thick fluid was observed. The mucous mem-

brane was covered with multiple papillary growths throughout its extent. The growths had not broken through the wall.

The left kidney weighed 240 Gm. Its capsule stripped easily, leaving an irregularly nodular but smooth light red cortical surface in which there were whitish mottled zones of varying size, representing small abscesses. The ureter



Fig 3—*A*, right renal pelvis (surgical specimen) showing the papillary character of the growth. The cells are of the characteristic transitional epithelial type. *B*, urinary bladder revealing the papillary characteristic growth of transitional epithelium (postmortem specimen, nine years later). Note that the degree of malignancy is similar to that observed in the renal pelvis and in the ureter. *C*, papilloma of the right ureter. Many of the cells are exfoliated from post-mortem changes. *D*, section of the lung, showing metastasis. Hematoxylin and eosin stain, $\times 75$.

was dilated. It was thin walled and light red and contained turbid urine. The mucous membrane was smooth. It was obstructed in its lower third from the extrinsic pressure of tumor masses in the pelvis.

The bladder was thick walled and contracted. Within the lumen there were only clotted blood and degenerated tissue. The mucous membrane was ulcerated at many points and was transformed into papillary growths of varying size which hung into the lumen. The area of the trigon and the region of the ureteral orifices were ulcerated. Here the usual landmarks were almost destroyed.

The prostate gland was normal. The tissues around the bladder and prostate, especially laterally and posteriorly, were infiltrated with new growth which was continuous with the growths along the iliac vessels.

Microscopic Findings The tubules and glomeruli of the left kidney were generally hypertrophied. There were also areas of polymorphonuclear neutrophilic infiltration. These involved tubules and other zones, which were sharply circumscribed in the form of abscesses.

The right ureter showed a neoplastic papillary growth of transitional type epithelium extending from the wall into the lumen. The epithelial cells were well differentiated.

The prostate showed chronic pyoprosstatitis.

Sections across the ulcer in the stomach revealed the base to be composed of necrotic tissue and pyogenic membrane with fibrosis beneath.

The liver revealed passive congestion of the central venous areas and new growth of transitional type epithelium in local well defined zones.

The bladder revealed areas of ulceration with incrustation, chronic infection and a papillary type of well differentiated transitional epithelial new growth.

The lungs exhibited edema, congestion and nodules of new growth composed of the transitional type of epithelium.

The aortic lymph nodes were involved by metastatic new growth similar to that observed in other metastases.

Anatomic and Microscopic Diagnosis—The following diagnoses were made

- 1 Scar of ancient right nephrectomy (nine years old) for papillary carcinoma of the renal pelvis, grade 2
- 2 Metastasis to the right ureter, the urinary bladder, the pelvic and aortic lymph nodes, the liver, the lungs and the pelvic bones
- 3 Compensatory hypertrophy of the left kidney (weight, 240 Gm)
- 4 Obstructive hydronephrosis and hydroureter on the left, with acute pyelonephritis and milary abscesses
- 5 Hypertrophy of the heart (weight, 600 Gm), hypertension (clinical)
- 6 Edema and congestion of the lungs with terminal bronchopneumonia
- 7 Chronic passive congestion of the liver, with focal and central necrosis
- 8 Edema of the legs (pressure of tumor on iliac veins and vena cava)
- 9 Chronic cystitis and pyoprosstatitis
- 10 Chronic ulcer of the stomach

PATHOLOGIC DISCUSSION

In the case presented the chief points of clinical interest as revealed by autopsy were as follows. The patient, who was 46 years old at death, had had a nephrectomy nine years previously for papillary

carcinoma of the right renal pelvis. The ureter had been divided just below the renal pelvis, although the growth was already extensive and had apparently spread beyond the pelvis. At necropsy there was no evidence of local recurrence in the fossa of the right kidney or in the tissue surrounding the right ureter. However, the mucosal lining of the ureter was the site of numerous papillary excrescences extending from the blind upper end to and into the bladder but nowhere breaking through the coats of the ureter. It is probable that the recurrence and extensions came from these malignant papillomas of the right ureter, first extending into the urinary bladder where multiple malignant papillomas were produced and subsequently involving the regional lymph nodes of the pelvis, the periaortic lymph nodes, the liver and the lungs.

The left kidney was hypertrophied, compensating the loss of the right kidney. The compensatory changes apparently had been adequate until terminal pyelonephritis secondary to obstructive hydronephrosis, hydronephrosis and encrustation cystitis aided in deciding the fatal outcome. There was also terminal bronchopneumonia.

Also of interest but probably not related to the pathologic changes in the urinary tract was the fact that the patient had cardiac hypertrophy apparently on the basis of severe hypertension, the specific cause of which was not elicited by autopsy¹⁶. Associated with the cardiac hypertrophy and dilatation there were terminal cardiac decompensation with edema of the lungs and chronic passive congestion of the liver with areas of focal and central necrosis. The pressure of the pelvic tumor mass about the vessels as they entered or came from the left leg was important in producing tremendous swelling of the left lower extremity.

SUMMARY

A case of papillary carcinoma of the pelvis of the right kidney is presented, together with a brief review of the literature.

The significance of the spread of this particular tumor down the ureter and the necessity of complete resection of the ureter at the time of nephrectomy are emphasized.

Several Detroit hospitals at which the patient was treated and several surgeons who treated him permitted the use of their records in the compiling of the data presented.

¹⁶ The surgical specimen removed nine years before death showed on microscopic examination "some tubular nephrosis and glomerular congestion in the substance of the kidney."

IMPORTANCE OF SIMPLE ULCER OF THE RIGHT SIDE OF THE COLON IN DIAGNOSIS OF ABDOMINAL DISEASE

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Opportunity to study 6 instances of so-called simple ulcer of the cecum and ascending colon has made evident the seriousness of this relatively rare lesion and the complications which it causes. A knowledge of the attendant symptoms is of especial importance for all those concerned with the diagnosis of abdominal disease, because of the bizarre symptoms, the gravity of the complications which usually ensue and the accompanying high mortality. Direction of attention to the cecum when inflammatory disease of the right lower quadrant of the abdomen is present is especially important whenever the diagnosis of appendicitis is uncertain or the appendix is known to be absent. That the diagnosis is difficult is evident from the fact that it was made correctly before operation in only 1 case reported in the literature¹. A correct pre-operative diagnosis was not made in any of my cases. Nevertheless, familiarity with the condition has convinced me that the diagnosis should be made preoperatively, at least in some instances, and that operation may be better conducted if the surgeon suspects the possibility of such a lesion at the beginning.

The term simple ulcer of the cecum is a misnomer. The condition is not simple in diagnosis or in treatment, and its cause is unknown. Ulcers of the cecum have been called "simple" when they are not associated with tumors, chronic ulcerative colitis, generalized arteriolar disease of the gastrointestinal tract or infection by specific organisms. These specific infections include *Endamoeba histolytica*, *Balantidium coli*, actinomycetes, tubercle bacilli and dysentery, typhoid and paratyphoid bacilli. Infection of the intestine and colon by the beta hemolytic streptococcus may result in a suppurative process similar to phlegmonous gastritis². The diagnosis of simple ulcer has been made by the pathologist after exclusion of other conditions of known causation or of other

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1 Bombi, G. Un caso di ulcera semplice del cieco. Studio clinico e radiologico, Policlínico (sez. prat.) **36** 1550, 1929

2 Cutler, E. C., and Harrison, J. H. Phlegmonous Gastritis, Surg., Gynec. & Obst. **70** 234, 1940

recognized entities. Ulcers for which this term is appropriate, however, resemble one another in most respects, though it is by no means certain that the condition is an entity. In fact, the ulcerations of the cecum associated with uremia (when these are not based on arteriolar disease) bear a strong resemblance to simple cecal ulcers. Both forms are of unknown pathogenesis, but it is to be presumed that the mode of development is different.

Although simple ulcer of the cecum has been known since the time of Cruveilhier,³ its cause remains entirely unknown. Recent studies have thrown important light, however, on the incidence, clinical features and pathologic anatomy. Among these are the papers of Quenu and Duval,⁴ Soupault,⁵ Barron,⁶ Wise,⁷ Wilkie,⁸ Bombi¹ and Cameron.⁹ Osler¹⁰ mentioned 2 instances of ulcer of the cecum, both with perforation, which were observed by him. A detailed description of these cases did not appear in the literature.

Cameron⁹ has pointed out that such ulcers have occurred at ages varying from 18 to 70 years. The condition is twice as common in men as in women. Although he found that a large proportion of the recorded cases have occurred in Scotland and France, my cases from the United States and Sweden, as well as those of others (Barron^{6a} and Bombi¹), indicate that the condition may be encountered over a much wider geographic area. That diet is a factor of uncertain importance is indicated by the fact that some authors⁹ have considered such disturbances to be common among persons in whose diet there is a preponderance of cereal grains, and Wilkie⁸ expressed the belief that diseases of the cecum have increased with the substitution of meat for vegetables in the diet. There were no unusual dietary habits among the 6 patients whose cases are reported in this paper.

3 Cruveilhier, J. *Anatomie pathologique. Maladies des intestins*, Paris, J. B. Bailliere, 1835-1842, vol. 2, pt. 30, plate 3.

4 Quenu, E., and Duval, P. *L'ulcere simple du gros intestin*, *Rev. de chir.* **26**: 692-713 and 792-831, 1902.

5 Soupault, R. *Contribution a l'etude de la perforation de l'ulcere simple colique*, *Rev. de chir.* **58**: 480, 1920.

6 Barron, M. E. (a) *Simple Nonspecific Ulcer of the Colon*, *Arch. Surg.* **17**: 355 (Sept.) 1928, (b) *Simple Nonspecific Ulcer of the Colon*, *Surg., Gynec. & Obst.* **50**: 870, 1930.

7 Wise, W. D. *Perforating Simple Ulcer of the Colon*, *Ann. Surg.* **93**: 1273, 1931.

8 Wilkie, D. *Simple Ulcer of the Ascending Colon and Its Complications*, *Surgery* **1**: 655, 1937.

9 Cameron, J. R. *Simple Nonspecific Ulcer of the Cecum*, *Brit. J. Surg.* **26**: 526, 1939.

10 Osler, W. *Principles and Practice of Medicine*, ed. 8, New York, D. Appleton and Company, 1915, p. 521.

Simple ulcer of the cecum usually occurs on the mesial aspect a few centimeters beyond the ileocecal valve. Although several authors have compared this location in relation to the ileum with that of duodenal ulcer in relation to the stomach, there is no sudden chemical alteration in the cecum comparable to that which occurs in the gastric contents when the latter pass into the duodenum. Cameron⁹ has stated that the relatively poor blood supply in this region of the cecum may be a predisposing factor. No significant vascular lesions have been found by the pathologist studying these cases. Barron,⁶ Bolton¹¹ and others have concluded that the frequent presence of gastric ulcer in patients who also have ulcer of the cecum means that the two conditions are local manifestations of a general pathologic disturbance and that the same etiologic factor may be the cause of ulcer on any segment of the gastrointestinal tract. Barron^{6a} pointed out that simple ulcer may occur on any part of the alimentary tract, from the esophagus to the rectum. The possible neurogenic origin of such lesions has long been a matter of speculation and investigation. The experimental evidence indicating that stimulation of the gastric secretory fibers in the vagus nerves may produce a secretion of gastric juice in the empty stomach and this in turn be followed by acute ulcers¹² suggests that a similar investigation of the lower part of the gastrointestinal tract might be of significance regarding the cause of simple ulcer of the colon.

Study by microscope leaves the nature of the ulcers as much a mystery as does mere inspection. The edges of the ulcers are rather sharp, and there is usually a small amount of connective tissue reaction. Extensive scarring is encountered only in cases of chronic and subacute involvement. Sometimes the edges of the ulcer are almost reactionless. The intestinal wall at the base is thinned even in the absence of perforation. Lymphocytes and polymorphonuclear leukocytes are present about the ulcer, but usually only in moderate numbers. However, in case 4 (this paper) an extensive suppurative reaction was manifested by the presence of many leukocytes and clumps of bacilli and cocci (fig. 3). There are no definite lesions of the adjacent blood vessels. It is unfortunate that there are few studies of the intestinal flora of these patients. There is nothing to suggest a relation to regional ileitis or lymphogranuloma in the present knowledge of the pathology of this lesion. However, if perforation does not occur, one would expect these ulcers either to heal completely or to evolve into a chronic state with accompanying fibrosis and cicatrization. Wilensky¹³ has expressed the belief that the granu-

11 Bolton, C. Ulcer of the Stomach, London, Edward Arnold, 1913, pp. 35-36.

12 Osler, W. Principles and Practice of Medicine, revised by H. A. Christian, ed. 13, New York, D. Appleton-Century Company, Inc. 1938.

13 Wilensky, A. O. The Essential Nature of Non-Specific Granulomatous Lesions of the Gastro-Intestinal Tract, Surgery 6: 452, 1939.

omatous lesions of the intestinal tract represent an end result of intestinal infection marked by secondary or final intramural infection and subsequent attempted overproductive but unsuccessful healing. On the basis of this assumption it has been suggested by Cutler¹⁴ that so-called simple ulcers of the cecum may be an antecedent or initial lesion of cicatrizing enteritis.

The clinical features of simple cecal ulcerations are usually not clearly defined. Cameron⁹ could find no really pathognomonic sign. In cases without complications there is usually a history of constipation with occasional melena. There may be vague, dull pain in the lower part of the abdomen, but it is seldom sufficiently characteristic to be of assistance in the diagnosis. One such uncomplicated ulcer of the cecum was excised,⁹ the patient making an uneventful recovery. The only pre-operative diagnosis of ulcer of the cecum on record was made by studies of the gastrointestinal tract after a barium sulfate enema, resection was performed, and recovery ensued.¹

Attention is usually directed to simple ulcer of the cecum, however not by symptoms due to the ulcer itself but by those caused by some complication. Wilkie⁸ has reported several cases which are of especial interest because of the variety of complications encountered. In 1, there was moderate hemorrhage. In another subacute perforation led to pericolicitis and the formation of a dense mass resembling a neoplasm. Resection of the cecum was performed, the impression being that the lesion was a true neoplasm, its actual nature was discovered only after the specimen was studied carefully. In a third case, stenosis of the cecum had resulted from cicatricial contraction of adhesions about the base of an old ulcer. A fourth patient had an acute perforation and died of generalized peritonitis. Wilkie⁸ also pointed out that a mass resembling an incarcerated hernia may be present in the inguinal region as a result of the slow perforation of a cecal ulcer.

Acute perforation is the most frequent and also the most dangerous complication of simple cecal ulcer. If the ulcer perforates into the peritoneal cavity, rapidly spreading peritonitis inevitably results, usually followed by death. However, Quenu and Duval⁴ and Zickler¹⁵ have reported recoveries after prompt closure of the perforation. Perforation of a simple ulcer of the cecum must be differentiated from the other causes of perforation, which may be neoplastic, traumatic, congenital (e.g., a diverticulum) or due to other types of infection. There was a mortality of 57 per cent in the series of 21 instances of perforated cecal ulcer summarized by Cameron⁹. Of the 6 patients on whom operation

14 Cutler, E. C. Personal communication to the author.

15 Zickler, H. Ueber einen Fall von Perforation des Colon ascendens, *Beitr z klin Chir* 67 189, 1909.

was not performed, all died, of the 15 patients on whom operation was performed, 9 recovered and 6 died

A correct diagnosis was made by means of a barium sulfate enema in the case of Bombi's¹ patient, mentioned previously. The pre-operative diagnoses which have been made are, in the order of their frequency: appendicitis, peritonitis, cholecystitis, cecal carcinoma, tuberculosis of the cecum, intussusception, intestinal obstruction, subphrenic abscess and postoperative ileus. The signs of perforation of a cecal ulcer could not be differentiated from those of perforation of an acutely inflamed appendix. Christian¹² has stated: "Perinephric and peri-cecal abscess from perforation of ulcer, either simple or cancerous, and circumscribed peritonitis in this region from other causes, rarely can be differentiated until an exploratory incision is made." However, the history may furnish important data which may give a lead as to the correct diagnosis. Whereas perforation of the appendix is always preceded by a period of abdominal discomfort, progressive in severity and often followed by a short period of subsidence of pain, acute perforation of the cecum occurs as a sudden intra-abdominal crisis of excruciating pain located initially in the right lower quadrant. The pain differs from that of perforation of a peptic ulcer only by an early difference in its location and absence of a characteristic history of a preceding gastric or duodenal lesion. Both lesions are always followed by signs of spreading peritonitis. Cholecystitis is less difficult to differentiate on account of its tendency to produce primarily localized symptoms referable to the upper part of the abdomen without evidence of peritonitis. Acute pancreatitis is usually preceded by attacks of indigestion, and a careful history elicits the story of recurrent attacks of milder abdominal pain before the severe crisis occurs. Also, with this disease, pain in the back is often prominent. Intussusception is primarily a disease of childhood and when it occurs in the adult is usually associated with a neoplasm of the bowel. One would not have difficulty in differentiating this lesion from an acute perforation of the bowel, but a slowly progressing chronic perforation of the right side of the colon might easily simulate an intussusception by producing a mass which is brought to the attention of the patient by sudden pain. In considering a diagnosis of tuberculosis of the cecum, one should search carefully for other foci of this infection and remember that every chronic lesion of the cecum and ascending colon is not necessarily due to this disease or to neoplasm. An unnecessarily radical operation might be avoided by this realization and by careful evaluation of all information available before and at operation.

As a perforated duodenal ulcer which drains down the right paravertebral gutter may present prominent symptoms and signs referable

to the right lower abdominal quadrant several hours after the initial attack, attention may be primarily drawn to this region. Again, one must rely on carefully taken history to furnish important differential diagnostic data. Patients with duodenal or gastric ulcer nearly always give a history of digestive upset which may or may not be characteristic of ulcer. Those having primarily ulceration of the lower part of the intestinal tract usually have disturbances of the lower part of the bowel, such as diarrhea, melena or constipation, but not the regular discomfort of peptic ulcer. A plain roentgenogram of the abdomen may show gaseous distention of the cecum and of the terminal portion of the ileum, as in case 1 of this series. The presence of a bubble of gas under the right side of the diaphragm is almost pathognomonic of perforated duodenal ulcer. However, it is quite possible that such a phenomenon might be present with perforation of a cecal ulcer. In case 3 this was true as the result of a subphrenic abscess following perforation of the hepatic flexure of the colon.

It is of especial importance to differentiate a simple ulcer of the cecum with perforation into the retroperitoneal tissues from carcinoma, because of the difference in surgical procedure indicated. Perforations caused by carcinoma are usually slow in onset. The dense scar tissue about a cecal ulcer with subacute perforation may closely simulate carcinoma, as in the case reported by Wilkie.⁸ The resemblance is even more complete when bits of intestinal contents escape and become encapsulated on the peritoneal surface. The similarity between these and carcinomatous implants may be striking, as was noted by Sampson.¹⁶

Differentiation between chronic ulceration of the cecum and ascending colon and regional ileitis may be difficult. The history and results of examination, as in case 4 of the present series, may be similar. Characteristic roentgen findings may be observed in advanced cicatrizing enteritis that establish the diagnosis. However, the final differentiation may not be made until laparotomy is performed.

Of the following 6 cases of simple ulcers of the right side of the large bowel, cases 1, 2, 3 and 4 are from the Peter Bent Brigham Hospital. Cases 5 and 6 were contributed in a personal communication by Dr. Clarence Clafoord from the clinic of Dr. Knute Giertz at the Sabbatsberg Sjukhus, Stockholm, Sweden.

REPORT OF CASES

CASE 1—A physician aged 32 was admitted to the hospital with a diagnosis of right ureteral calculus two hours after the onset of severe pain which radiated from the right lower quadrant of the abdomen to the pubic region. He was doubled

¹⁶ Sampson, J. A. Implantation Peritoneal Carcinomatosis of Ovarian Origin, *Am J Path* 7:423, 1931.

up by pain and said that he felt as though "something had burst inside." He was nauseated but did not vomit. In spite of urgency to urinate, he was unable to void.

Four years previously, right renal colic had been relieved after the delivery of a calculus from the right ureter by cystoscopic manipulation. Two years previously, appendectomy had been performed during an episode of pain in the right lower quadrant of the abdomen. It was said that the appendix was mildly inflamed at



Fig 1 (case 1) —Results of a barium sulfate enema nine weeks after perforation of the cecum. There is incomplete filling of the cecum and ascending colon. At fluoroscopy there was spasm of the cecum and barium could not be forced through the ileocecal valve.

that time. Two weeks before the present illness he had had an attack of diarrhea and vague abdominal pain, which was thought to be due to food poisoning. After several days the bowel movements became normal, and all discomfort ceased until the onset of the present attack. There was no history of dysentery, but he had been exposed to *Balantidium coli* during an epidemic in North Carolina.

On physical examination the patient appeared to be in great pain. His temperature was 99.6 F by rectum. The abdomen showed moderate resistance

in the right lower quadrant, with tenderness at the scar of the McBurney incision. The leukocyte count of the blood was 18,000 per cubic millimeter, 85 per cent of the cells were polymorphonuclears. By catheterization 500 cc of normal urine was obtained. A roentgenogram of the abdomen showed normal renal shadows. The cecum was distended by gas. During the next hour, signs of peritoneal irritation became definite, with increasing muscular spasm and rebound tenderness always referred to the McBurney scar. The picture was that of perforation of an acutely inflamed appendix, but the appendix had been removed two years before. There was no palpable mass, and peristalsis seemed to be increasing. A diagnosis of early intestinal obstruction due to postoperative adhesions was therefore made, and operation was performed. A right rectus incision liberated a large amount of free purulent fluid from the peritoneal cavity. A smear showed numerous leukocytes but no organisms. The cecum and the terminal portion of the ileum were acutely inflamed, and a considerable amount of fibrin was present over the surface of the former. There was no evidence of intestinal obstruction. When the cecum was lifted, several hundred cubic centimeters of purulent fluid was aspirated from the right iliac fossa. No diverticula were seen or felt. A well healed appendectomy scar was identified. There were no enlarged mesenteric lymph nodes. Three centimeters above the ileocecal valve, on the mesial wall of the cecum, there was an area of acute inflammation surrounded by adherent fat, in the center of which was a hole about 2 mm in diameter. There was no foreign body present which could have caused perforation. A probe passed gently into this opening entered the lumen of the cecum. There was no palpable mass in the cecal wall suggestive of carcinoma, acute inflammation with slight thickening of the wall being the only demonstrable lesion. The perforation was closed and turned in with two inverting purse string silk sutures. The peritoneum was closed without drainage, the skin and subcutaneous tissues were not sutured. Constant gastric suction was necessary for three days in order to combat intestinal ileus.

Culture of the peritoneal fluid yielded *B. coli* and a nonhemolytic streptococcus. These organisms were also found in the purulent material from the superficial wound infection. Sulfanilamide was administered for four days after operation. Repeated examinations of the stools showed no amebas or *Balantidium coli*. Agglutination tests for typhoid, paratyphoid, and *Brucella melitensis* gave negative results. The temperature did not exceed 101 F, and the patient was well, except for a localized wound infection, three weeks after operation. A barium sulfate enema five weeks later showed spasm and irritability of the cecum, the barium could not be forced through the ileocecal valve (fig 1). The rest of the colon was normal. A gastrointestinal roentgenographic series made three months after operation showed nothing abnormal. Six months after operation the patient was well and free of symptoms.

CASE 2—A man aged 70 years was admitted to the hospital complaining of urgency and frequency of urination of three years' duration. In addition, a history of repeated gastrointestinal upsets consisting of flatulence, epigastric discomfort and vomiting was obtained. A diagnosis of diverticulosis of the descending colon and sigmoid had been made by means of a barium sulfate enema eight months previously, the cecum appeared normal. At the same time, a gastrointestinal roentgenographic series showed no abnormality of the stomach or of the small intestine. The patient was found to have an enlarged prostate, with retention of urine. After six days of constant drainage of the urinary bladder, a suprapubic prostatectomy

was performed. On the second postoperative day the abdomen became distended, and no gas or fecal material was passed by rectum. In spite of everything that could be done, the abdomen remained "as tight as a drum and silent as a tomb." The patient died on the fifth day after operation. The nonprotein nitrogen of the blood rose to 46 mg per hundred cubic centimeters and the leukocyte count to 19,000 per cubic millimeter.

At autopsy three chronic gastric ulcers were found near the pyloric end of the stomach. None of these had perforated, and there was no evidence of hemor-



Fig 2—Photomicrograph (hematoxylin and eosin stain, $\times 165$) showing an ulcer in the cecum covered by a fibrinopurulent exudate and infiltrated by leukocytes. There is a thrombosed vein in this zone of inflammation.

rhage from them. Six centimeters above the ileocecal valve, lying on the lateral wall of the ascending colon, there was a hemorrhagic and necrotic ulcer 3.5 by 2.5 cm. Its peritoneal surface was covered by necrotic material and fibrinous exudate. About 2 cm superior and posterior to this ulcer there was a second ulcer, slightly smaller but similar. The entire wall of the upper portion of the cecum and the lower 8 to 10 cm of the ascending colon were hemorrhagic and friable. The transverse, descending and sigmoid colon showed diverticula which were not inflamed. All the diverticula had demonstrable openings into the colon.

Microscopic examination of sections of the cecum and ascending colon showed extreme inflammation of all layers (fig 2). There was a fibrinopurulent exudate over the mucosa in some places. The tunica muscularis and serosa were infiltrated with polymorphonuclear leukocytes, lymphocytes and monocytes. Some of the vessels of the submucosa were filled with fibrinous thrombi in the area of inflammation, but this was thought to be a result rather than a cause of the process, since no vessels out of the zone of inflammation were thrombosed. In the regions of ulceration the mucosa and submucosa were absent. The surrounding fat showed infiltration by leukocytes and many bacteria. Fibroblastic proliferation was seen in the cecal wall and surrounding fat. Other sections from the transverse and descending colon showed edema of the serosa and infiltration by leukocytes. A satisfactory explanation of the condition of the cecal wall was not apparent. Amebic infection was not present. The changes were not those of infarction secondary to occlusion of the mesenteric vessels. The patient died as a result of peritonitis secondary to perforation of an ulcer of the cecum.

CASE 3—A man aged 56 years came to the hospital with a diagnosis of right subphrenic abscess and left hemiplegia. For years the patient had suffered from indigestion. Two months previously he had had pneumonia, from which he had not recovered completely. The left hemiplegia occurred during convalescence and led to his entry to the hospital. The patient was pale and poorly nourished. There was no demonstrable motion of the right side of the diaphragm, rales were heard at both pulmonary bases, the heart was moderately enlarged, the abdomen was normal to palpation, and there was flaccid paralysis of the left side of the body. Fluoroscopic examination showed a large bubble of gas beneath the right side of the diaphragm and a fluid level visible near the costal margin. Rib resection and drainage of the subphrenic abscess were performed with the region under local anesthesia. The patient had bronchopneumonia and died twelve days after operation. At autopsy a perforation of the hepatic flexure of the colon was observed. The colon was adherent to the anterior abdominal wall, gas and feces escaped through the opening in the colon into the subphrenic abscess. The perforation was so walled off from the rest of the general peritoneal cavity by the omentum that the intestines remained normal. There was no evidence of ulcerative colitis, diverticula of the colon or carcinoma. The ileum was normal. One could only presume that a primary ulcer of the hepatic flexure had caused the perforation, with subsequent subphrenic abscess and death.

CASE 4—A woman aged 23 years came to the hospital on account of repeated attacks of abdominal pain, nausea, vomiting and diarrhea which had occurred infrequently for two years. However, for two weeks the attacks had been more frequent and more severe and in addition had been accompanied by pain on urination. Forty-eight hours before admission she was awakened by acute epigastric pain and felt violently nauseated. She vomited repeatedly, and diarrhea was severe. There was no hematemesis or melena. The past history was non-contributory. Appendectomy had been performed ten years before.

The temperature was 102.8 F, and the patient was dehydrated. She was in moderate pain but did not appear ill. There was generalized tenderness to deep palpation over the entire abdomen, but no significant localized tenderness and no muscle spasm. There was tenderness in both flanks posteriorly, but neither kidney was palpable. Pelvic examination revealed no abnormality. The leukocyte count of the blood was 14,000 per cubic millimeter, and the catheterized urine contained 15 leukocytes per high power field. Gastric analysis and gastrointestinal roentgenographic series revealed no abnormality. At cystoscopic examination an acute

inflammation of the bladder and a moderate hydronephrosis of the right kidney were found. Cholecystograms showed evidence of a pathologic gallbladder. A barium sulfate enema disclosed a smooth constriction 15 cm above the ampulla of the rectum. The bowel proximal to this was normal and a film taken after evacuation showed satisfactory emptying. Examination of the stool showed no blood or pus.

After one week of study, exploratory laparotomy was performed by Dr. John Homans through a right rectus incision. The entire abdominal cavity was explored.



Fig 3—Photomicrograph (eosin-methylene blue, $\times 165$) showing an ulcer of the cecum with superficial erosion of the mucosa and a shelving edge of fibrinous exudate. There is extensive infiltration of leukocytes, red cells, fibrin, clumps of bacilli and cocci.

The cecum and ascending colon were covered by adhesions. The ascending colon was bound down just below the hepatic flexure by a mass of old adhesions, which might have been congenital or inflammatory. The bowel was narrowed but not obstructed at this point. The cecum and ascending colon were not reddened but the wall was thickened. There were several large lymph nodes close to the cecum. The cecum and ascending colon were removed, and an end to side anastomosis of the ileum to the transverse colon was performed. The patient made an uneventful recovery.

The surgical specimen consisted of a resected portion of the ileum 5 cm long, the cecum and 19 cm of the ascending colon. There was marked congestion of the serosa, and several injected mesenteric lymph nodes were included. An irregular stellate ulcer measuring 2 cm in its greatest dimensions was present on the anterior wall of the cecum, just at the ileocecal valve. In the cecum and ascending colon were numerous smaller ulcers, 2 to 4 mm in diameter. These were covered with a layer of reddish fibrinous exudate. No diverticula were present. Microscopic sections of the cecum (figs 3 and 4) showed a normal muscle wall and serosa. The



Fig 4—Same as figure 3, $\times 300$

mucosa was superficially eroded in many places and replaced by ulcers with shelving edges made up of a fibrinous exudate, with many polymorphonuclear leukocytes, red cells, fibrin, clumps of bacilli and cocci. The capillaries of the muscularis were dilated. The lymphoid follicles were hyperplastic. The diagnosis was acute ulcerative cecitis, probably bacterial in origin (figs 3 and 4).

CASE 5—A woman aged 65 had suffered for several years with vague attacks of abdominal pain and constipation. A roentgenographic diagnosis of gallstones was made, but operation was deemed unwise. Two days before her admission to the hospital, there occurred abdominal pain, nausea and vomiting. When she

was first seen her general condition seemed to be good. The temperature was 38 C., and the pulse was strong. The whole right side of the abdomen was tender, but evidence of peritonitis was lacking. After forty-eight hours of observation, severe acute abdominal pain began on the right side, followed by signs of spreading peritonitis. The patient passed quickly into shock, the skin was cold, clammy and cyanotic. However, after six hours she responded to a transfusion of blood and infusion of saline solution. Operation was performed and a perforation of the cecum about 5 cm. above the ileocecal valve was found. There was no evidence of tumor or diverticulum. The perforation was sutured and the abdomen closed. The patient died three days later from peritonitis.

CASE 6—A woman aged 35 suffered from intermittent attacks of diarrhea and constipation for several years. A diagnosis of tuberculosis of the cecum was made by means of a barium sulfate enema. Right colectomy was performed, with end to end ileocolostomy. Pathologic examination showed several ulcers of the cecum and ascending colon with no evidence of tuberculosis, granuloma, typhoid, paratyphoid or dysentery. The patient was later operated on for intestinal obstruction but has since been quite well. The diagnosis by the pathologist was simple ulcer of the cecum.

COMMENT

Perforation of the bowel occurred as a result of the inflammatory process in 4 of the cases in this series. Case 1 was an instance of a sudden intra-abdominal crisis in a young man, due to perforation of the cecum by localized inflammation. Prompt operative closure of the perforation resulted in recovery. In case 4 the patient, a young woman, had repeated attacks of diarrhea, abdominal pain, nausea and vomiting. No abnormalities were demonstrated by roentgen examination, but at operation a definitely abnormal cecum and ascending colon were found, and the resected bowel showed several acute ulcers, probably of bacterial origin. This case is strikingly similar to one reported by Wilkie. In case 6 successful resection of the right side of the colon was carried out by Dr. Crafoord for three simple ulcers which simulated tuberculosis on roentgen examination. In case 5 operation was performed after forty-eight hours' observation, and a perforation of an ulcer of the cecum was closed. The patient was old and succumbed to the peritonitis which had progressed rapidly. In cases 2 and 3 perforation of ulcers of the ascending colon was discovered at postmortem examination.

Roentgenographic barium enema studies were made in 4 of the 6 cases cited here. It is apparent that in the present state of knowledge the correct diagnosis cannot be made by this means of study alone, but it may contribute valuable evidence. In case 1 a barium enema given nine weeks after operative closure of a perforation of the cecum showed persistent spasm and poor filling (fig. 1). In case 2, six months before perforation of the cecum and death, barium studies of the entire gastrointestinal tract had demonstrated no abnormality. In case 4 a barium

enema given several days before operation failed to show evidence of several acute ulcers which were present in the cecum and ascending colon. The roentgenographic diagnosis in case 6 was inflammatory lesion of the cecum, interpreted as being tuberculous in origin.

Owing to the apparent rarity of this disease, little has been learned about it since it was first described, one hundred years ago. As the complications arising from it are attended by such a high mortality, it is imperative that simple ulcer of the cecum be considered in the differential diagnosis of the "acute abdomen." Perforation of such a lesion may simulate perforation of an acutely inflamed appendix or may exhibit a picture closely resembling appendical abscess. Differentiation from a perforated gastric or duodenal ulcer may be difficult. A right rectus incision would usually be the approach of choice. Decision in favor of simple closure of the perforation or resection of the ascending colon can be made only at operation.

SUMMARY

Six patients with simple ulceration of the cecum or ascending colon have been described. The difficulties of clinical diagnosis, the serious nature of the complications of the condition and its wholly unknown etiology and pathogenesis indicate that this kind of intestinal ulceration deserves considerably more investigation than has so far been made.

NOTE—Since this article was submitted for publication, an interesting case of simple ulcer of the cecum has been published by Moore.¹⁷ In this instance, at operation the lesion was thought to be a neoplasm and resection of the entire ascending colon was carried out. The patient made a satisfactory recovery.

¹⁷ Moore, T. Simple Non-Specific Ulcer of the Ascending Colon, *Brit J Surg* **27** 600 (Jan) 1940.

INTRATHORACIC NEUROFIBROMA

A BRIEF REVIEW OF THE LITLRATURE AND REPORT OF ONE CASE

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Tumors within the chest are more often discovered now, since the use of roentgen rays has become frequent. During the past few years more attention has been given to these lesions, since the great progress in thoracic surgery has brought about the possibility that benign intrathoracic tumors, particularly, may be successfully approached and removed.

Prior to the use of modern methods of diagnosis of intrathoracic conditions, many tumors were undiagnosed, and only those coming to autopsy were brought to light. Therefore, few benign intrathoracic tumors were correctly diagnosed during life and recorded in the literature.

Of the benign tumors within the chest which have been reported, many were described as originating from nerve tissue elements or structures adjacent to spinal nerves or the sympathetic nervous chain. Although during the past two decades the subject has received more consideration than before, the literature as yet lacks considerable information that undoubtedly would aid in a better understanding. A typical benign intrathoracic tumor is demonstrated in the following case, observed by us.

REPORT OF CASE

M P, an obese white woman aged 56, was ill for two weeks in March 1939 with influenza. During this illness she had not received the attention of a physician but had remained at her home in bed until the acute symptoms of the disease had subsided. Two weeks after the onset of the illness she presented herself for an examination with the complaints of frequent coughing, weakness, poor appetite, exhaustion on moderate exertion and a dull and somewhat intermittent pain in the right side of the chest in the region of the upper and outer quadrant of the right breast. During the attack of influenza she had had a dry and nonproductive cough, but after a few days transparent, mucoid sputum had been raised, occasionally streaked with bright red blood. Before onset of the influenza she had been in apparently good health and had been able to do her usual housework without any noticeable discomfort except that occasionally she had noticed the dull and intermittent pain in the upper lateral portion of the right side of the chest for about one year. This pain, however, had never been of

great enough intensity to cause her much concern. She had not noticed any pain in the shoulder or the right arm, but at times she thought that she had felt a dull and aching pain at the lower angle of the right scapula. There had been no dyspnea, orthopnea, change in the voice, disturbance in the right eye or the eyelids or sensation of weight or heaviness in the right side of the chest.

Physical Examination—The height was 5 feet and 5 inches (165 cm), the weight 196 pounds (89 Kg), the temperature 98.6 F, the pulse rate 80 and the respiratory rate 22 per minute. The pupils were equal, round and regular and reacted to light and in accommodation. The eyeballs were equally prominent. The eyelids were not abnormal. The neck was short, and there was no engorgement of its veins or visible pulsation of its vessels. The thyroid gland was not palpable. Deviation of the trachea was not noticeable, and a tug was not present. The head moved normally in all directions, and there was no evidence of imbalance of the muscles of the neck. The chest was thick and well padded with fat. Over the anterior part of the chest on both sides the percussion note was resonant. Respiratory sounds were normally heard over the anterior part of the chest, and the voice was not remarkable. The breasts were pendulous but of equal size and free from masses. Examination of the posterior part of the chest revealed relative dullness to percussion over the thick muscles in the upper portion on both sides, and the breath sounds were not as distinctly heard as over the anterior part. The excursion of the lungs at the bases in the posterior part of the chest was apparently normal, and the percussion note was bilaterally resonant over that area. Rales were not heard in any part of the chest. The spine was slightly tender to deep jarring over the thoracic portion, but a definitely localized painful area could not be determined. The heart was in a normal position and without apparent enlargement. The heart sounds were distinct, the rhythm was regular and no murmurs were present. The mediastinal dullness seemed to be within normal limits. The blood pressure in both arms was 140 systolic and 90 diastolic. Examination of the abdomen, rectum, genitalia and extremities revealed no significant findings. A neurologic examination, which included inspection of muscular development and function and tests of the reflexes and sensations was without remarkable findings. The skin was free from lesions and was everywhere smooth and soft.

Roentgen Examination—A roentgen examination of the chest was advised merely as a routine procedure because of the lack of significant physical findings.

Stereograms of the chest were made. A large mass was present in the upper part of the right side of the thorax. It appeared to extend from the midline well into the upper part of the right side of the chest, involving a considerable portion of the upper lobe of the right lung. The trachea was pushed toward the left but apparently was not compressed to any appreciable degree. The right pulmonary field below the mass and the left pulmonary field appeared clear. There was no evidence of pleural effusion in either thoracic cavity. The border of the mass in the upper part of the right side of the chest was well defined and oval. A lateral roentgenogram of the chest revealed the mass to be in the posterior and upper portion. The bony thorax, the heart and the aorta appeared relatively normal (fig. 1).

Routine Laboratory Examination—The erythrocyte count was 4,050,000, with 80 per cent hemoglobin, and the leukocyte count 5,800, with 62 per cent neutrophils, 36 per cent lymphocytes and 2 per cent eosinophils. The Kahn test was negative. The urine had a specific gravity of 1.006, an acid reaction and no sugar or albumin. Microscopic examination of a catheterized specimen revealed an occasional epithelial cell.

Operation—About one month later, after the patient's complete recovery from influenza, operation was done (May 19, 1939)

The patient was placed on the table on her left side with the right side uppermost and the right arm extended somewhat above her right shoulder. Intra-pharyngeal administration of nitrogen monoxide and ether was used to induce anesthesia. An incision about 9 inches (23 cm) in length was made between the spine and the medial border of the right scapula in the posterior part of the right side of the chest, beginning about 2 inches (5 cm) below the level of the spine of the seventh cervical vertebra and curving laterally to a point over the seventh rib. The trapezius and rhomboideus muscles were divided and the right scapula retracted laterally. The second, third and fourth ribs were identified and exposed from the costovertebral junctions to a point slightly beyond their angles. Their periosteum was incised and stripped from them from the costovertebral junction to a point within their respective angles and their freed portion removed. The intercostal muscles were divided and the pleura exposed. Beneath the space thus

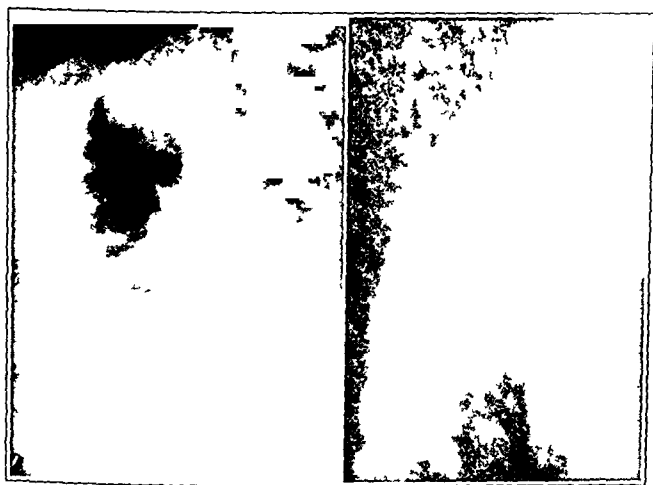


Fig 1—Left, roentgenogram showing the large oval shadow in the upper part of the right side of the thorax. The trachea is pushed to the left. Right, lateral roentgenogram, showing the mass in the upper posterior part of the thorax.

made in the upper posterior part of the right side of the chest a stony hard mass could be felt beneath the pleura. It was obvious that the pleura overlying the mass must be incised in order to reach it, and this was done. The mass was completely covered by pleura, which it had pushed well into the right pleural cavity, and compressed the upper lobe of the right lung to a considerable degree. By careful dissection with the gloved hand the mass was easily separated from the lung and was found to be attached by a pedicle about the diameter of a lead pencil to a point opposite the second intervertebral foramen and about 1 inch (2.5 cm) lateral to it. When the tumor was then divided at its pedicle with the electrocautery there was no active bleeding. Delivery of the mass through the space which had been made by the resection of the portions of the second, third and fourth ribs was not possible, so that the fifth rib was exposed, incised near its costovertebral junction and retracted downward, after which the tumor was easily delivered. Inspection at the site of the attachment of its pedicle revealed that it apparently had originated from structures about 1 inch (2.5 cm) lateral

to the right second intervertebral foramen. There was no deformity, indentation or erosion of the vertebrae and no evidence that the pedicle of the tumor had penetrated the intervertebral foramen. The right lung, which had not completely collapsed, was reexpanded by positive pressure and the pleura closed with catgut.

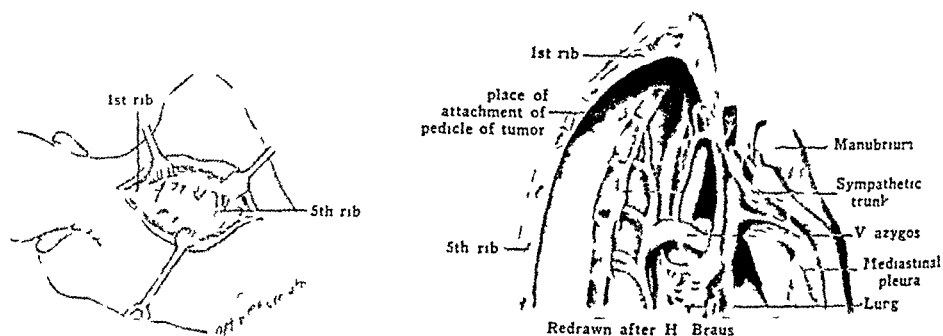


Fig 2—Left, diagram showing the position of the wound made. Right, diagram of the relative position of the intrathoracic structures on the right and the point of attachment of the tumor, which has been removed.

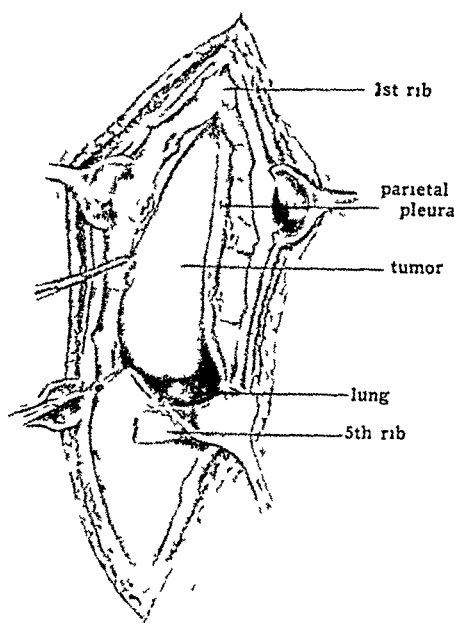


Fig 3—Appearance of the tumor on the opening of the posterior parietal pleura.

without difficulty. The remaining wound was closed in layers without drainage, catgut being used for the muscles and interrupted silk sutures for skin (figs 2 and 3).

Postoperative Course—Recovery was uneventful, and the patient was discharged from the hospital on the sixteenth day. A roentgen examination of the chest two days before discharge revealed the right lung to be normally expanded, without

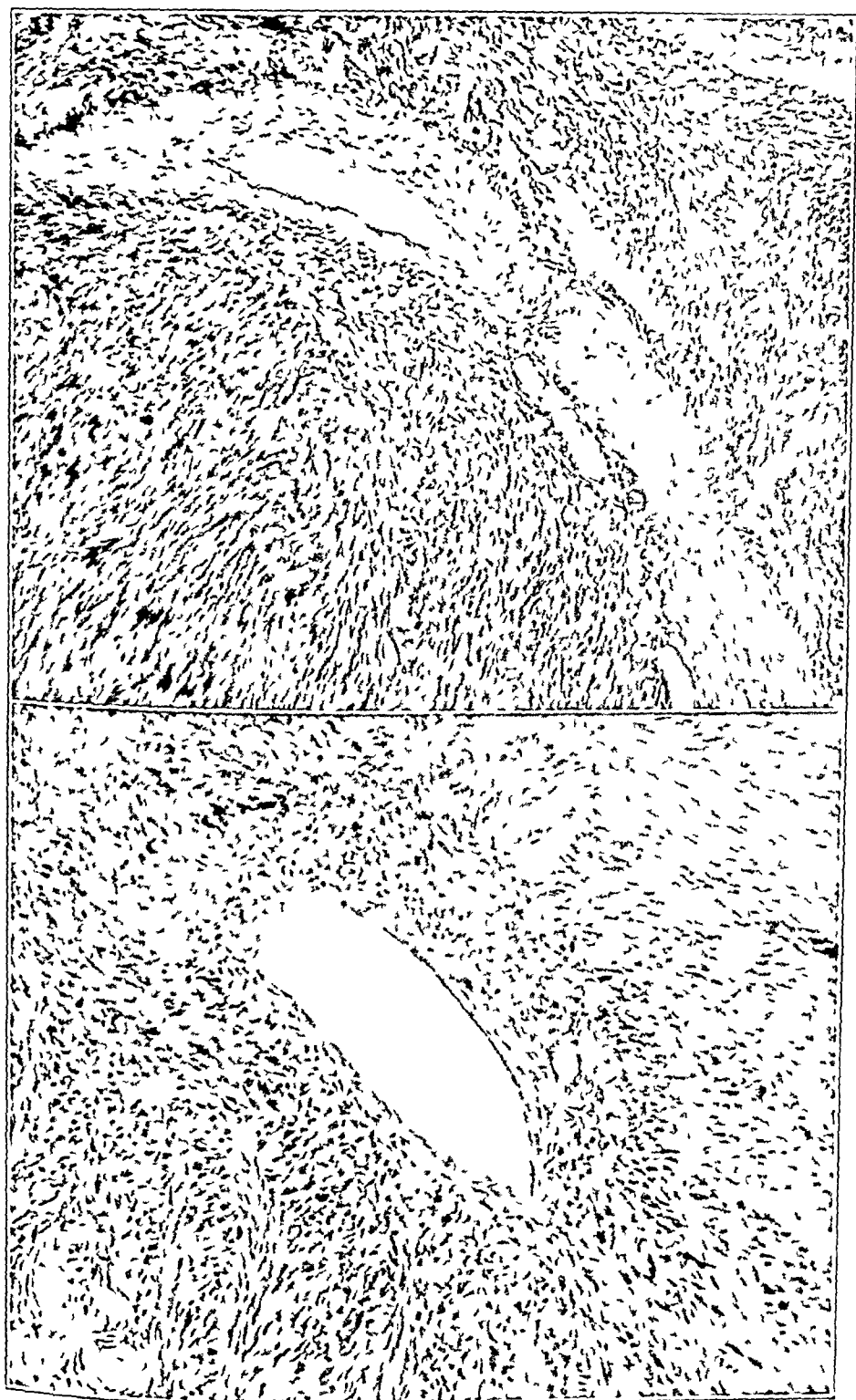


Fig 4—Above, photomicrograph of the neurofibroma removed from the upper posterior part of the right side of the chest, showing 'palisading' and hyaline thickening of the wall of a blood vessel. Below, photomicrograph of the neurofibroma, demonstrating wavy fibers (right upper corner) and rat-bearing areas around a thin-walled vessel in the left upper corner.

evidence of pleural effusion. The wound had healed by first intention, and dressings were not required after the tenth postoperative day.

Pathologic Picture—The specimen was examined by Dr. H. R. Prentice, whose report was as follows: "The specimen received was solid, firm, ovoid, 11 by 8 by 6 cm. and well encapsulated. At one pole was a pedicle of connective tissue about 2 cm. across and 0.8 cm. long, which had been severed by cautery. This appeared to arise from the peripheral layers of the capsule and have no gross connection with the tumor."

The cut surface of the tumor was grayish and semitranslucent, with scattered, opaque, yellow areas.

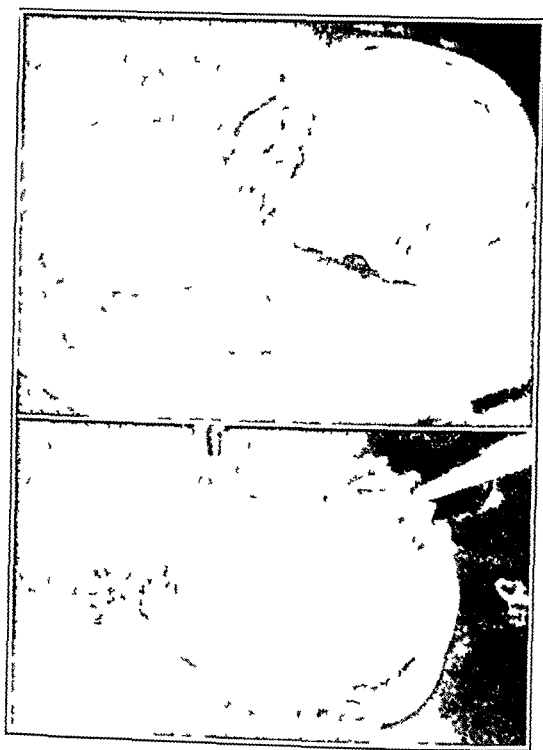


Fig. 5—Above, gross appearance of the tumor, which measured 11 by 8 by 6 cm., and the resected portions of the second, third and fourth ribs. Below, the tumor cut open to demonstrate the grayish and semitranslucent center and the thick capsule.

Microscopically, the tumor showed partly the slender, wavy fibers and slender nuclei which characterize neurofibromas. In other areas there was a denser structure, with palisading of nuclei, and a tendency to the formation of whorls by cells with nuclei which varied from a slender, elongated form to a plumper form. In some of the plump cells the nuclei were multiple. There were no mitoses. The stroma was vascular, and some of the small vessels showed marked hyaline thickening of their walls (figs. 4 and 5).

The pedicle showed only somewhat edematous connective tissue. There was no evidence of neoplastic invasion.

The general arrangement was orderly, and the tumor was considered benign histologically and in the manner of its growth. It was noted, however, that if removal had not been complete, local extension would have had to be feared.

The tumor fell in the class of intrathoracic tumors of neurogenic origin. It had in part the characteristics of neurofibroma—that structure occurring in the grossly white, semitranslucent areas—while in the yellow portions it had the appearance of the tumor which has been variously called neurinoma, perineurial fibroblastoma, lemmoma or schwannoma.

Penfield¹ noted that this combined histologic picture may occur and suggested that perineurial fibroblastoma may occur within a neurofibroma, replacing the tissue of the latter to the edge. Verocay² noted that the two types of structure may be associated and suggested the term "neurinofibroma." This is perhaps the best designation for the tumor here examined.

Follow-Up Record—Three months after her discharge from the hospital the patient was seen and found to be entirely free from the pain in the back and

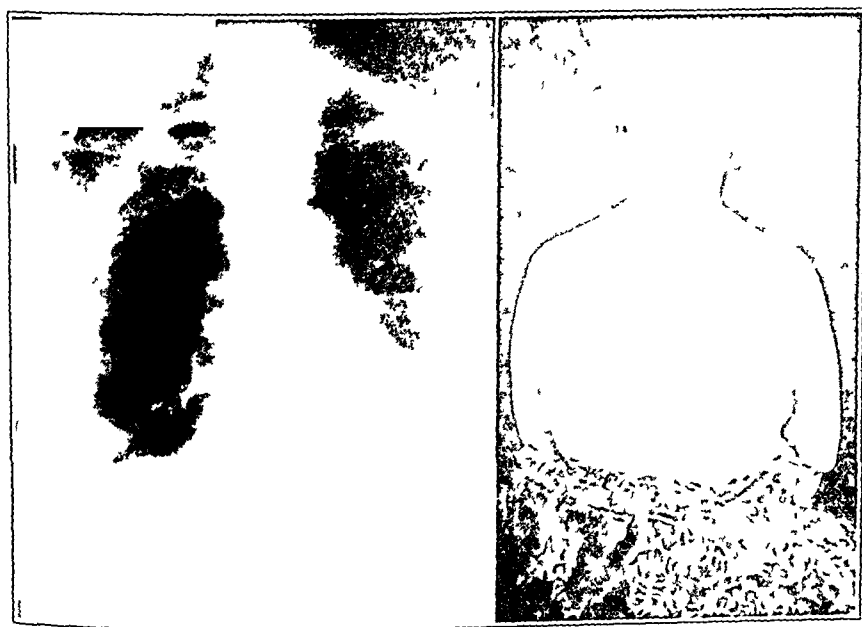


Fig 6—Left, roentgenogram of the chest three months after the removal of the tumor, showing normal expansion of the right lung and regeneration of the resected ribs. Right, photograph showing the operative scar.

the right upper and lateral thoracic region. She had regained her normal strength and was able to do her usual housework without discomfort. A roentgenogram of the chest was made at that time and revealed that the right lung was normally expanded and the right pleural cavity clear. The mediastinum appeared normal, and the resected ribs in the upper posterior part of the right side of the chest had regenerated. In January 1940 the patient seemed well and offered no complaints (fig 6).

¹ Penfield, W. Encapsulated Tumors of the Nervous System, Surg, Gynec & Obst 45 178, 1927.

² Verocay, cited by Kaufmann, E. Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co, 1929, vol 3, p 2030.

COMMENT

This case seems to be an excellent one to exemplify how silent a benign thoracic tumor may be, as the condition was discovered only accidentally by roentgen examination. Overholt and Souders³ recently reported somewhat similar cases (1 case of intrathoracic fibroma and 1 case of ganglioneuroma in younger persons), in 1 of which mild symptoms were apparently present for two years before the thoracic tumor was discovered. Adams⁴ stated that physical examination is of little value except when percussion reveals a widened area of dullness in the chest and that diagnosis is made chiefly by fluoroscopic and roentgenologic studies.

The pathologic diagnosis of the tumor in our case is neurofibroma which was located extrapleurally and paravertebrally in the upper part of the right side of the chest. Because of its location and histologic structure it resembles closely the hourglass tumors which have been described by Heuer.⁵ The hourglass tumors include a great variety of pathologic conditions, but they arise from a fairly restricted region and pathologically include tumors which most often are neurogenic. Of 64 hourglass tumors which Heuer collected from the literature up to the year 1929, 37 involved the dorsal spinal cord, the thorax or the mediastinum. Six of the tumors were neurofibromas, 5 neuroinomas, 5 neuromas, 5 ganglioneuromas and 5 fibrosarcomas, and the remainder of the group limited to the dorsal region included chondrosarcomas, sarcomas and some of which the pathologic diagnosis was uncertain. Heuer found that 5 of the 37 tumors were entirely within the spinal canal, whereas 30 were both paravertebral and within the spinal canal and 2 were paravertebral only. The last 2 occupied the mediastinum and presented a pedicle which entered the intervertebral foramen, but the intraspinal tumor was not sufficiently large to produce symptoms of compression of the spinal cord.

A brief summary of 2 cases (one of Cushing's and one of Guleke's) from Heuer's series follows:

Cushing's Case—A woman aged 48 for ten years had pain in the right side of the back below the scapula. There were no symptoms of compression of the cord. The patient had point tenderness to the right of the spine at the level of the fifth thoracic vertebra. Roentgen examination showed a rounded mass projecting from the mediastinum toward the right at the level of the second interspace anteriorly and the sixth and seventh ribs posteriorly. There was slight angulation of the dorsal vertebrae at the level of the tumor. Operation was done.

3 Overholt, R. H., and Souders, C. R. Benign Intrathoracic Tumors, *S. Clin. North America* **17** 905, 1937.

4 Adams, H. Tumors of the Mediastinum, *S. Clin. North America* **18** 629, 1938.

5 Heuer, G. J. The So-Called Hour-Glass Tumors of the Spine, *Arch. Surg.* **18** 935 (April) 1929.

in two stages, with approach to the mediastinal tumor from behind. A nodular tumor which was fixed to the side of the vertebral column was removed. It was not positively determined that the tumor did not enter the intervertebral foramen. The patient recovered but continued to have pain in the right side and in the back when she vomited. She was killed five years later in an automobile accident.

Guleke's Case—A woman aged 33 for five years had a drawing sensation in the right side of the chest and had difficulty in lying on the right side. Infection of the upper part of the respiratory tract associated with a cough and dyspnea developed, which lasted for three weeks and did not entirely clear up. Roentgen examination of the chest revealed a large mass in the right side, which was sharply defined and extended from the fourth to the tenth rib. A large portion of the eighth, ninth and tenth ribs was resected, with marsupialization of the pleura in the first stage, and one month later a large tumor was resected. It was attached by a small pedicle, which disappeared into an intervertebral foramen. The patient recovered after postoperative development of empyema and was in good condition four months after operation.

The structure of our tumor, as of the hourglass tumor, indicated that the origin was probably from a spinal nerve or the fibrous structures, ligaments or periosteum within or near the intervertebral foramen of a spinal nerve.

Harrington⁶ studied 46 intrathoracic tumors, of which 11 were proved to be neurofibromas on microscopic examination. Ten of these were situated in the posterior mediastinum, whereas the other was on the left thoracic wall along the course of the ninth intercostal nerve. A brief summary of 1 of Harrington's cases, which closely resembles our case, is as follows:

Harrington's Case—A woman aged 53 had pains in both sides of the chest on coughing and on deep breathing. Physical examination gave essentially negative results. Roentgen examination of the chest showed a shadow in the right side of the mediastinum at the level of the fourth and fifth ribs. At operation the approach was posterior, through a space made by the resection of the fourth and fifth ribs. The tumor was situated in the upper posterior part of the right side of the mediastinum, to the right of the aorta, and at the level of the third intercostal space it was attached to the body of the vertebra. This patient made an uneventful recovery and was discharged from the hospital on the twenty-eighth postoperative day.

Overholt and Souders³ in 1937 grouped the benign intrathoracic tumors as follows: (1) dermoids and teratomas, (2) fibromas, neurofibromas, perineural fibroblastomas and ganglioneuromas, (3) osteomas, chondromas and osteochondromas, (4) myxomas, (5) lipomas, and (6) hemangiomas, cystic hygromas and lymphangiomas. They expressed the opinion that the most numerous and the most important of these groups are the first two. They stated:

[The tumors of the second group] are _____ found posteriorly in the thorax, _____ along the gutter between the ribs and the vertebrae, adjacent to _____

⁶ Harrington, S. W. Surgical Treatment in Fourteen Cases of Mediastinal or Intrathoracic Perineural Fibroblastoma, *J. Thoracic Surg.* 3: 590, 1934.

the sympathetic nerve chain. Occasionally they approach the intervertebral foramina and sometimes grow through this opening into the spinal canal when they assume the dumb-bell shape and are prone to cause neurologic symptoms.

These are among the most silent tumors in the thorax and some cause no symptoms whatever.

Solitary neurofibromas have been less commonly encountered within the thorax than within the skull, where they are frequently attached to the acoustic, optic or trigeminal nerve, or within the spinal canal, where the point of origin is usually a posterior root.

Penfield¹ explained that the solitary neurofibroma or perineurial fibroblastoma is an encapsulated tumor attached to a spinal nerve root or to a cranial nerve and is centrally located, whereas the neurofibromas of von Recklinghausen are usually multiple and involve the peripheral nerves. In the differentiation of the solitary neurofibroma and the multiple neurofibromas of von Recklinghausen's disease it must be remembered that the origin of the tumors is essentially the same, in that the growths seem to arise

from the specialized investment which separates and insulates nervous tissue from the rest of the body.

The multiple superficial tumors which appear in neurofibromatosis are an expression of a system disease. The condition shows marked hereditary tendencies.

The tumors of [neurofibromatosis] represent a thickening [of the nerves due to] a congenital abnormality in the structure of the peripheral nervous system.

Fibers of the nerve enter the tumor at one end and leave it at the other [there being a] connective tissue increase about the fibers of the nerve.

Because of this intermixture of nerve fibers with connective tissue, the term *neurofibroma* [indicates] *fibroma* on and in a nerve. In solitary perineurial fibroblastomata the normal nerve is applied to the capsule of the tumor without penetrating it.

Andrus,⁷ in tracing the derivation of various elements composing the nerves and ganglions of the thorax, pointed out that neurofibroma is "a tumor arising from a nerve and containing any or all of the constituents of the nerve trunk. Such tumors are thought to spring from the perineurial or endoneurial tissue."

Tumors may present themselves in many locations in the chest. However, neurogenic tumors obviously occur most often in the posterior thorax. For this reason, they are probably best approached operatively through the back of the chest. If there are symptoms of compression of the cord it is advisable to attack them by laminectomy, with the idea in mind that both the intraspinal portion and the intrathoracic portion of the tumor may be removed by the extension of the one incision.

⁷ Andrus, W. DeW. Tumors of the Chest Derived from Elements of the Nervous System, *J Thoracic Surg* 6:381, 1937.

When there are no symptoms of involvement of the spinal cord, it seems to be less hazardous and wiser to use the thoracic approach. Each individual case is a problem in itself, and the decision must be based on this fact. Harrington advised that pneumothorax should be induced three to five days preoperatively to adapt the patient to an open pneumothorax during the operation.

Benign intrathoracic tumors, although less frequently seen, are relatively more important than the malignant growths, because successful removal and cure are possible. When they are discovered within the chest, because of the frequency of their position in the upper and posterior portion of the thorax, the surgical approach and exposure need not be too difficult. A complete extirpation may be the rule rather than the exception, and the postoperative course, even in elderly patients, may be essentially uneventful. Early and complete removal of such tumors is of the greatest importance, not only because their gradual enlargement may result in serious pressure within the thorax but also because of the possibility of sarcomatous degeneration, which has been proved to occur.

SUMMARY

- 1 A case of intrathoracic neurofibroma is reported in which the growth was discovered accidentally by roentgen examination in a woman aged 56.

- 2 A favorable surgical approach to benign lesions of the upper posterior part of the thorax is described in detail.

- 3 The incidence and pathologic picture of intrathoracic neurofibroma are briefly reviewed and discussed.

- 4 The prognosis for surgical treatment is debated.

INFLUENCE OF BONE ASH ON THE REPAIR OF BONE

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OMAHA

AND

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In a previous publication¹ there was presented experimental evidence that bone ash aided ossification. In the reported experiments transplants of osteogenic tissue were cultured in the anterior chamber of the eye in a medium saturated with bone ash. It was suggested that the minerals used in the formation of bone exist in bone and in bone ash in a physicochemical form particularly suitable for use in the process of ossification.

To examine this evidence further, the influence of bone ash on the repair of fractures was investigated in a series of 11 rabbits. In the original series of 24, 13 were lost by death or infection.

METHOD

In each animal equal segments were removed from the shaft of each radius in total block resection, and to discourage repair small bits of costal cartilage were placed in the defects between the fragments. In addition to cartilage, bone ash derived from bones of other rabbits was used to fill the defect in each right radius. The left one contained only cartilage and served as a control for comparison. The process of repair was followed by means of weekly roentgenograms over a period of four weeks and examined post mortem at the end of this period.

RESULTS

There was failure of repair of 3 of the defects which contained bone ash and of only 1 of the controls. In most instances the callus which formed in the presence of bone ash was larger but less well defined and organized. Microscopically, in the specimens in which many particles of the ashed bone were still present there was some residual inflammatory reaction around and within the site of repair.

From the Departments of Physiology and Surgery of the University of Nebraska College of Medicine.

1 Bisgard, J D. Ossification. Influence of Mineral Constituents of Bone, Arch Surg **33** 926-939 (Dec) 1936.

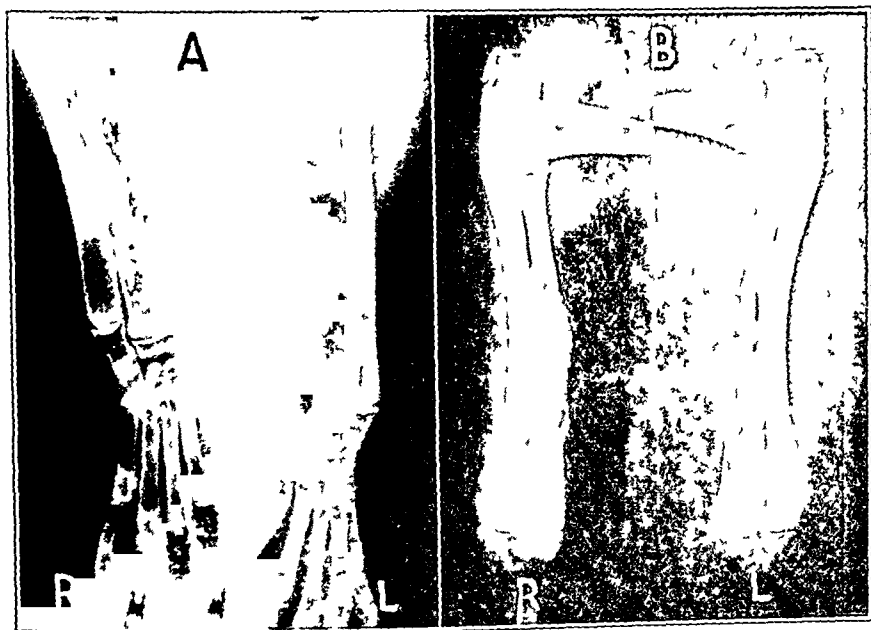


Fig 1—Roentgenograms of the radiuses of a rabbit *A* the day after the operation. Note bone ash in the defect in the right radius. *B*, four weeks later. Both defects have been repaired and there is firm union between the fragments. Note in *B* considerable bone ash and excessive callus in the right radius.

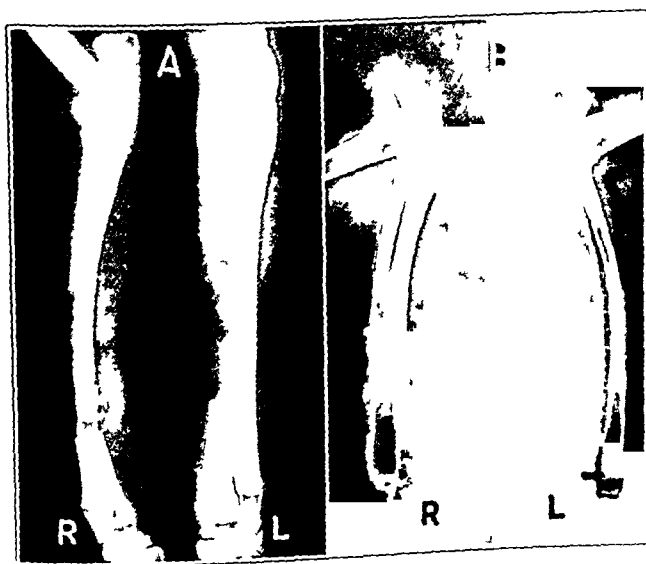


Fig 2—The radiuses of another rabbit *A*, the day after the operation and *B*, four weeks later. Although both defects are well repaired the left one, which had no bone ash, repaired more normally.

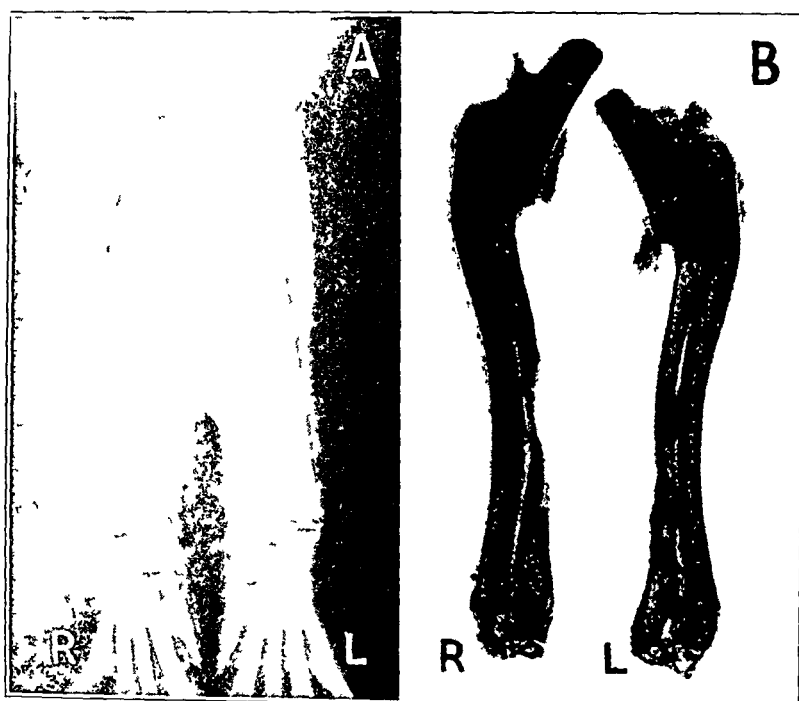


Fig 3—Roentgenograms of a rabbit in which there was failure of repair of the defect in the right radius, the one containing bone ash. In the left radius, the control, the defect repaired normally. *A*, the first, and *B*, the final, roentgenogram.

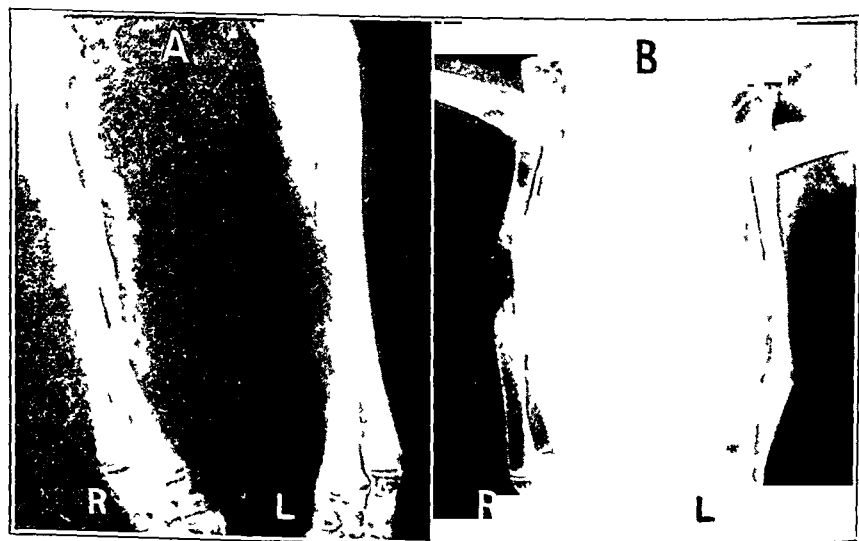


Fig 4—As in the rabbit of figure 3, so in the one shown in these roentgenograms: normal repair of the defect in the control radius and failure in the one containing bone ash. *A*, the earliest roentgenogram; *B*, the final roentgenogram.

In figures 1, 2, 3 and 4 are illustrated the first and last roentgenographic records of 4 representative animals

CONCLUSION

From these experimental data there is no evidence that bone ash aids the repair of bone. On the contrary, the evidence indicates that it may have a deleterious effect.

ADENOSQUAMOUS CARCINOMA OF THE PERIPAPILLARY PORTION OF THE DUODENUM

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AND

DAVID R MORGAN, MD

PHILADELPHIA

Adenosquamous and squamous carcinomas of the duodenum are exceedingly rare lesions, only 5 cases, 3 of the former and 2 of the latter, having been reported in the literature. Three of the growths were peripapillary, and the others were localized in the suprapapillary segment of the duodenum. One of these involved the common bile duct by extension. The purpose of this communication is to review the essential features of these cases and to record an additional example of adenosquamous carcinoma of the peripapillary portion of the duodenum.

REPORT OF A CASE

H C, a white man aged 49 years, entered the Elk County General Hospital, Ridgway, Pa., on Feb 24, 1932, with jaundice, fever and moderately severe epigastric pain of short duration. Roentgenograms showed what was interpreted as a defect, probably neoplastic, of the pyloric portion of the stomach. The symptoms subsided, and the patient returned to work at the end of two weeks. After a short interval jaundice reappeared, in association with clay-colored stools and dark urine. Subsequent complaints were eructations and a sense of abdominal distention after meals, accompanied by pain in the upper portion of the abdomen. The pain was severe at times but did not radiate. There was no vomiting, and the appetite remained good, yet the patient lost 40 pounds (18 Kg) during a period of three months. Roentgenographic examination was repeated on April 2 but showed no gastric defect, changes were observed in the gall-bladder which suggested a neoplastic process.

Physical Examination—The patient entered Jefferson Hospital on June 22 because of marked generalized itching. Examination showed a well nourished, deeply jaundiced subject. The liver was palpable 8 cm below the costal margin in the midclavicular line. It was moderately firm, tender and movable. No other masses were seen or felt, and there was no evidence of free fluid in the peritoneal cavity.

Laboratory Data—Roentgenograms of the gastrointestinal tract suggested the presence of an extraintestinal lesion in the upper portion of the abdomen, which

From the Pathological Laboratories of the Jefferson Medical College and Hospital, and the Department of Neoplastic Diseases

was interpreted as a pancreatic lesion, an enlargement of the liver or a new growth. A small amount of barium sulfate remained in the stomach at the end of six hours, indicating delayed emptying. The hemoglobin content of the blood was 62 per cent, the red cell count 3,690,000, the color index 0.84 and the white cell count 8,600 (polymorphonuclear neutrophils, 86 per cent). The urine was acid, brown to black, with a specific gravity of 1.010 to 1.016, a trace of albumin and occasional epithelial cells. It contained no sugar, no blood and no casts. The gastric contents showed a residual total acidity of 28, but no free hydrochloric acid, after a test meal these figures gradually rose to a maximum of 62 and 41 respectively at the end of forty-five minutes. Blood was present in the last gastric specimen, and lactic acid and bile were absent from all specimens. The stools were well formed, grayish brown and alkaline, and contained blood and considerable quantities of mucus, but no ova, no parasites and no excess of fats. The van den Bergh reaction was positive, biphasic, and the serum bilirubin was 11 mg, 80 per cent and 90 per cent respectively of bromsulphalein (2 mg dose) was retained at the end of thirty minutes on two occasions. The nonprotein nitrogen content of the blood was 34.32 mg per hundred cubic centimeters of blood. The Wassermann reaction of the blood serum was negative.

Course—At laparotomy on August 2 a greatly distended gallbladder was exposed, and 50 cc of white bile was aspirated. Palpation did not reveal the exact cause of biliary obstruction, which, however, was thought to be in the common bile duct. An anastomosis was established between the gallbladder and the stomach. Bleeding appeared postoperatively, the temperature rose from 96 to 106 F and the pulse rate from 60 to 120 per minute. The patient died the following day.

Postmortem Examination—Autopsy was performed eighteen hours after death and was limited to the abdomen. The combined gross and microscopic diagnoses were (1) adenosquamous carcinoma in the region of the papilla of Vater with obstruction to the common bile duct, hydrohepatosis and marked jaundice, (2) surgical cholecystogastrostomy, (3) chronic cholecystitis, (4) biliary cirrhosis of the liver, (5) hemoperitoneum, (6) cholemic nephrosis, and (7) bronchopneumonia.

Gross Examination The peritoneal cavity contained a large amount of liquid and clotted blood. The serosa was everywhere smooth and glistening, and the operative wound was clean. The kidneys, weighing 200 Gm each, were deeply jaundiced, and the cortex was markedly swollen.

The common bile duct and the cystic and hepatic ducts were considerably enlarged, the distention reaching into the finer intrahepatic radicles of the biliary system. The papilla of Vater was prominent, and the ring of tissue about its stoma was firm and fibrous-like. The pancreatic duct was not explored. Adjacent to the common bile duct, between it and the vena cava, was a lymph node the size of a lima bean. The gallbladder was distended with blood, and its wall was slightly thickened. A considerable quantity of blood and coffee ground flocculi were present in the stomach and duodenum. The liver, weighing 3,290 Gm, was soft, smooth and green, and section disclosed marked distention of the intrahepatic biliary ducts.

Microscopic Examination One section of the duodenum included the terminal segment of the common bile duct.¹ The wall of the duct was thickened by chronic inflammatory tissue, and the surface epithelium was partially autolyzed and desquamated. Approximately 0.5 cm from the termination of the common duct in the duodenum, a neoplastic growth was observed on the surface (fig 1). On

¹ This is known both as the ampulla of Vater and as the common bile duct, but in this communication it will be called by the latter designation.



Fig 1—Terminal end of the common bile duct, which is surrounded over a greater portion of its circumference by the duodenal mucous membrane. At the lower right is the orifice of the duct, and just behind this on each side are the nodular neoplastic excrescences ($\times 15$)

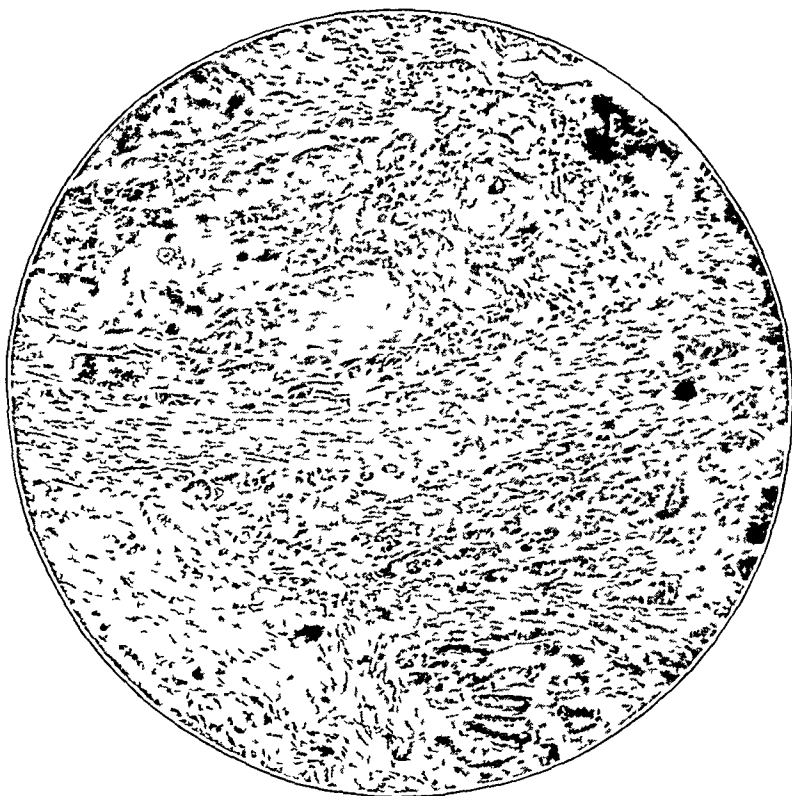


Fig 2—Intraduodenal segment of the wall of the common bile duct, showing epidermoid differentiation with pearl formation above and glandular differentiation below. Details are well brought out with the aid of a hand lens ($\times 100$)

one side this consisted of a flat plaque of infiltrating glandular epithelium arranged as acini, cords, nests and masses and, adjacent to this, a nodular villous projection composed of undifferentiated cells, epithelial pearls and acinous structures (figs 2 and 3). On the opposite side of the duct was an area of ulceration bordered by infiltrating, well differentiated epidermoid carcinomatous tissue. The duodenal mucous membrane surrounding the orifice of the common duct was somewhat autolyzed. Its deeper portion was infiltrated with tumor cells of the squamous and the glandular type (figs 4 and 5).

A second histologic section of the duodenum included a small wedge of fibrotic pancreatic tissue, an intramural segment of the duct of Wirsung and externally,



Fig 3—Wall of the common bile duct, showing mixed glandular and epidermoid differentiation ($\times 250$)

a portion of the common bile duct. Mixed glandular and epidermoid carcinomatous tissue was present in all coats of the duodenum, including the deeper portions of the mucous membrane, and in the wall of the main pancreatic duct, but none was observed in the pancreas or in the wall of the common duct at this level. The nerves and the perivascular lymphatics were also infiltrated in places.

The carcinomatous tissue was studied in numerous sections, some in serial arrangement. A composite description of the neoplasm follows. In some areas the tumor was composed of loosely arranged masses and columns of undifferentiated small cells which stained rather uniformly but varied in shape. Their nuclei were relatively large and of various shapes, and frequently showed mitotic figures, many of which were irregular. Concentrically laminated whorls were present, composed of keratin material, flat horn cells with eleidin granules, large pale

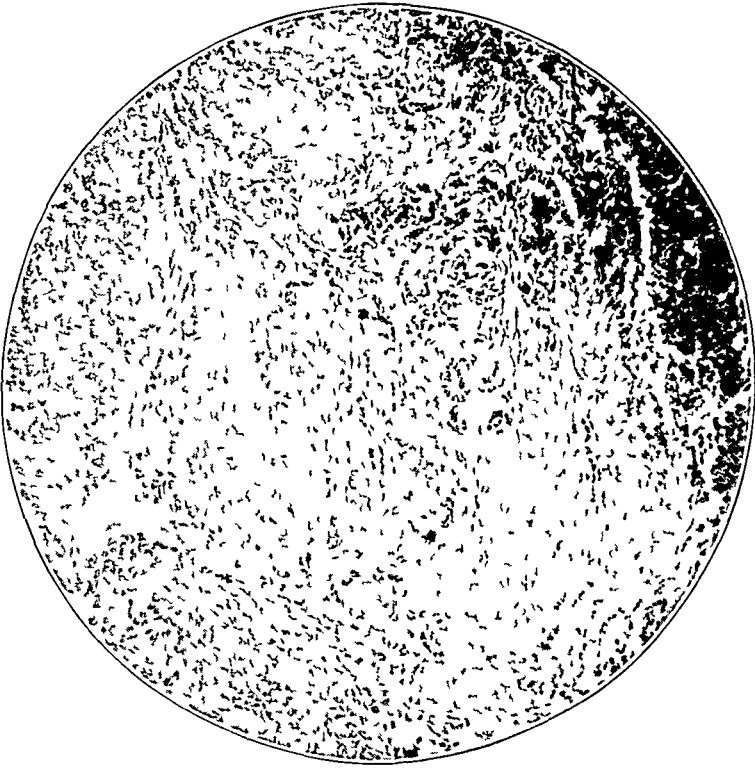


Fig 4—Muscular wall of the duodenum, showing small infiltrating neoplastic nodules ($\times 100$)

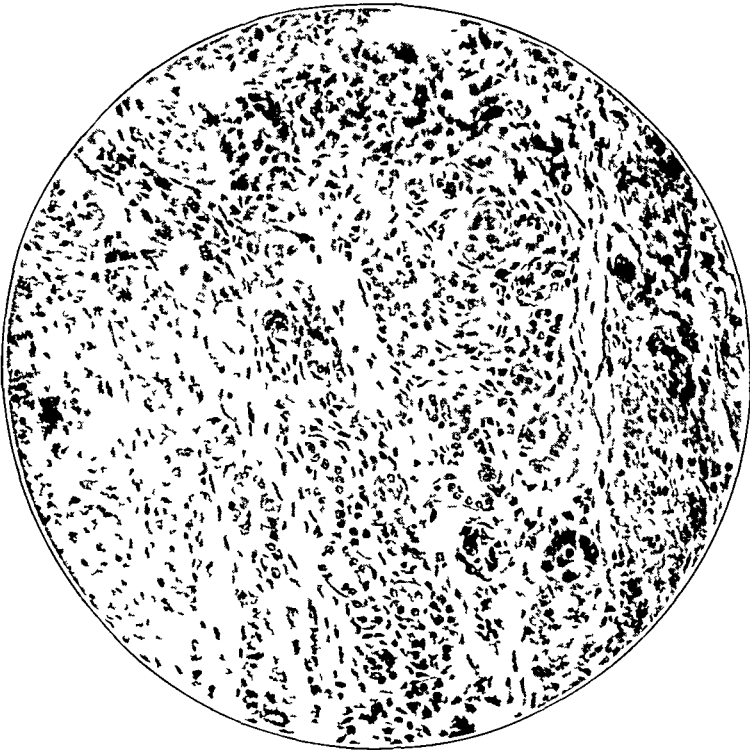


Fig 5—Higher magnification of the section illustrated in figure 4, showing the glandular type of growth composing an infiltrating nodule in the muscular wall of the duodenum ($\times 250$)

prickle cells with intercellular bridges and acidophilic inclusion bodies, and deeply stained small basal cells externally. The cells in these epidermoid areas were irregular in size, shape and staining qualities, and many mitotic figures were present, a large proportion of which were irregular and multipolar. In other areas the tumor showed a glandular structure with cuboidal or columnar cells arranged in the form of small or large, round or elongated acini, which occasionally contained degenerated material. These glandular cells were fairly uniform in appearance, with deeply stained granular cytoplasm and large, sometimes multiple nuclei showing frequent mitotic figures. Epidermoid, glandular and undifferentiated cells occurred independently, side by side or intermingled. In one area cells in a transition stage between glandular and squamous cells were observed in some of the large acini. Necrosis and hemorrhage were inconspicuous features. The stroma of the tumor was composed of adult, poorly vascularized connective tissue infiltrated with inflammatory cells.

Associated changes in the liver, gallbladder and kidney were of interest. The liver showed slight degeneration, necrosis and pigmentation of the cells of the inner portion of the lobule and rather marked fibrosis as well as small round cell infiltration of the portal radicles and considerable proliferation of the small bile ducts. The wall of the gallbladder was thickened by hypertrophied muscle and fibrous tissue, and there were many small hemorrhages as well as a few local collections of lymphocytes. The renal epithelium of the convoluted and Henle tubules showed marked degeneration, necrosis and biliary pigmentation. (The significance of these changes in the kidney following biliary obstruction and operative decompression of the biliary tract has been discussed by Lieber and Stewart².)

CASES FROM THE LITERATURE

*Plenge's Case*³—*Adenosquamous carcinoma of the peripapillary portion of the duodenum*

A man aged 54 years died with clinical manifestations suggesting carcinoma of the pancreas with obstruction of the biliary ducts. Autopsy revealed a large, centrally necrotic carcinoma of the duodenum about the papilla of Vater accompanied by infiltration of the head of the pancreas, obstruction of the common and the pancreatic duct and metastasis to the hilar and pancreatic lymph nodes, the liver and both lungs. The neoplastic growth consisted for the most part of strands and cords of flat cells varying in size and shape, and of scattered epithelial giant cells. These cells were frequently connected by intercellular bridges and occasionally formed epithelial pearls. In some areas, especially those adjacent to the normal duodenal mucosa, elongated and round acini lined by a single row of cuboidal and cylindric epithelium were observed. Elsewhere the lining cells were in part cylindric and showed transition to the pavement type. The metastases in the liver, lymph nodes and lungs also showed a mixture of adenocarcinoma and squamous carcinoma.

*Lageder's Case*⁴—*Adenosquamous carcinoma of the suprapapillary portion of the duodenum*

2 Lieber, M. M., and Stewart, H. L. Renal Changes Following Biliary Obstruction, Decompression and Operation on the Biliary Tract, *Arch Path* 19 636 (May) 1935.

3 Plenge, C. Beitrag zur Frage der Krebse mit ortsremdem Epithel, *Virchows Arch f path Anat* 264 370, 1927.

4 Lageder, C. Un caso di carcinoma parapilorico dimorfico del duodeno, con metaplasia epidermoidale e metastasi ovarica, *Clin med ital* 62 461, 1931.

A woman aged 49 years, complaining of jaundice, a sense of pressure in the abdomen, loss of appetite and insomnia, died two months after the onset of illness. Autopsy revealed an ulcerated tumor, 5 cm in diameter, in the posterior wall of the duodenum in its first and second portions. The first portion of the common bile duct was surrounded and obstructed by the neoplastic mass, but the ampulla of Vater was completely free. There were metastases to the liver, regional lymph nodes and right ovary. The tumor varied considerably in the different sections, being almost entirely scirrhous in some and cellular in others, and was accompanied by the formation of acini which occasionally showed papillary projections. In one section there were pronounced pleomorphism and hyperchromasia and numerous mitotic figures. Another section showed a transformation into epidermoid elements, with voluminous cells occurring singly and in groups of ten to twenty or more to form large plaques in the centers of which were fusion of cytoplasm and beginning keratinization.

*Matter and Hartman's Case*⁵—*Adenosquamous carcinoma of the peripapillary portion of the duodenum*

The patient was a man aged 54 years, with malaise, anorexia, low grade fever, jaundice, epigastric fullness and pain of seven months' duration. At laparotomy there was marked distention of the extrahepatic biliary passages, and a firm mass was palpated adjacent to the head of the pancreas. A cholecystostomy was performed, and the patient died two months later. At autopsy the ampulla of Vater was filled with a friable, grayish tumor mass which extended through the papilla onto the duodenal surface as a flat, rough, granular, nonulcerated nodule, 2 cm in diameter. There were extension to the head of the pancreas and metastases to the liver and the regional lymph nodes. Microscopic section of the tumor showed unusually large, irregular neoplastic glands lined by high columnar cells intermingled with solid masses of squamous epithelium well differentiated in places but with no distinct epithelial pearls.

*Cohen and Colp's Case*⁶—*Squamous carcinoma of the peripapillary portion of the duodenum*

A woman aged 47 years complained of progressively increasing jaundice, loss of weight, clay-colored stools and dark urine of two months' duration. At laparotomy the common bile duct was opened, and a probe was easily passed into the duodenum. The patient died eight hours after cholecystostomy. At autopsy the papilla of Vater appeared prominent and nipple shaped, and considerable force was required to pass a probe through its orifice, which was surrounded by a small firm mass of whitish tissue. There was an enlarged hard lymph node adjacent to the cystic duct. Histologic sections of the papilla of Vater showed instances of transition from spheroidal cells to typical squamous carcinoma.

*Schussler's Case*⁷—*Squamous carcinoma of the suprapapillary portion of the duodenum* (reported in tabular form only)

A man aged 75 years complained of colic lasting for four months and jaundice for four weeks. Autopsy revealed a stenosing carcinoma of hazelnut size

5 Matter, J G, and Hartman, F W. Primary Carcinoma of the Duodenum. Clinical and Pathologic Aspects, with Differential Diagnosis, J A M A 99 1853 (Nov 26) 1932

6 Cohen, I, and Colp, R. Cancer of the Peri-Ampullary Region of the Duodenum, Surg, Gynec & Obst 45 332, 1927

7 Schussler. Ueber das Verhalten der Gallenblase bei Choledochusverschlüssen, Beitr z klin Chir 115 433, 1919

immediately above the papilla of Vater, with extensive metastases in the liver and the lymph nodes. Slightly cornifying squamous carcinoma was the histologic diagnosis.

COMMENT

The incidence of the type of tumor dealt with in this communication is low. Of 416 cases of carcinoma of the peripapillary portion of the duodenum,⁸ in 222 the diagnosis was proved histologically, in these, 2 growths were of the squamous, and 2 of the adenosquamous, type, giving an incidence of about 10 per cent for each, or a total of about 2 per cent. Of 113 reported cases of carcinoma of the suprapapillary segment (Stewart and Lieber⁹), in 41 there were adequate clinical histories and gross and microscopic studies, of these 41 cases 1 each was of a squamous and an adenosquamous carcinoma, giving an incidence of 2.4 per cent for each.

In the present series, death occurred within two to seven months from the onset of symptoms, the average duration of illness in 5 cases being only four months. Three patients who were subjected to palliative cholecystostomy died eight hours, one day and sixty days, respectively, after operation. There were 4 men and 2 women, with ages ranging from 47 to 75 years, the average age being 54.6 years. All the patients exhibited jaundice, and 3 had abdominal pain. One or more of the following symptoms were also present: a sense of pressure in the abdomen, abdominal distention, loss of appetite, loss of weight, fever and eructations. The liver and occasionally the gallbladder were palpably enlarged and usually tender. However, a correct clinical diagnosis of the cause of the biliary obstruction was not made in any case. At autopsy, metastases were demonstrated in all 6 cases in the regional lymph nodes, in 4 cases in the liver and in 1 case each in the pancreas, lung and ovary.

The origin of the tumors situated in the suprapapillary segment of the duodenum was clearly from the duodenal mucous membrane, but the exact source of the Vaterian cancers was obscure. As the source of the latter, five possibilities exist, namely: (1) the duodenal mucosa covering the papilla of Vater, (2) Brunner's glands, (3) the cells lining the terminal end of the common bile duct, (4) those lining the corresponding portion of the pancreatic duct and (5) those lining the ampulla of Vater, when that is present. Because of the complex arrangement, the normal anatomic variation and the intimate relationship of the structures in this small area, together with the tendency for early neoplastic

8 Lieber, M. M., Stewart, H. L., and Lund, H. Carcinoma of the Peripapillary Portion of the Duodenum, *Ann Surg* 109: 219 and 383, 1939.

9 Stewart, H. L., and Lieber, M. M. Carcinoma of the Suprapapillary Portion of the Duodenum, *Arch Surg* 35: 99 (July) 1937.

spread, it is practically impossible to determine the exact point of origin of tumors in the region of the papilla of Vater.

The genesis of squamous or adenosquamous cell carcinoma in this region is unknown. The theory that such tumors may be the result of overgrowth from, or inclusion of, adjoining epithelium of a different type is unsatisfactory, since the distance from the esophagus, the nearest structure normally lined by squamous epithelium, is too great to admit of this possibility. Such neoplasms have also been ascribed to ectodermal rests or inclusions of indifferent cell masses exhibiting postembryonic growth. Metaplasia offers a more obvious and rational explanation, since it may occur in chronically inflamed tissues, especially when they are subjected to chemical or mechanical irritation, such as that inflicted by stones in the biliary ducts. In the series of cases under consideration there is lack of information bearing on this point, although it was stated that cholecystitis was present in 3 cases and gallstones in 1. Several hypotheses have been suggested in explanation of the occurrence of glandular and pavement epithelium in the same neoplasm. The tumor may arise in previously normal glandular epithelium which reverts to a more primitive stage of differentiation (anaplastic metaplasia). Other possibilities include (1) heterotopia of squamous cells followed by partial differentiation to a higher stage (progressive metaplasia or prosoplasia) and (2) a multicentric origin from heterotopic squamous cells and the adjacent, previously normal glandular epithelium.

SUMMARY

A case of adenosquamous carcinoma of the peripapillary portion of the duodenum is reported. Five additional examples of heterologous metaplasia in this region are reviewed.

GASTRIC CRISIS OF TABES DORSALIS

TREATMENT BY ANTERIOR CHORDOTOMY IN EIGHT CASES

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Surgical treatment of the gastric crises of tabes dorsalis has only recently offered promising and definite results. It is now recognized that the usual types of antisyphilitic therapy have little effect on such crises. Stokes¹ stated that "marked amelioration of symptoms is possible in 24 per cent, the usual response consisting in reduction in severity and length of attack with or without an increase of intervals between them—Fever therapy and especially malaria often afford striking temporary relief and the response may even be prolonged."

In outlining intelligently any form of surgical therapy, one must take into account the physiology and the pathologic physiology involved. At present, concepts concerning the physiologic mechanism of visceral pain are controversial, so that in a measure surgical efforts have been of the trial and error type. Indeed, it is more likely that the results of carefully controlled clinical experiences will solve certain physiologic problems than that animal experimentation will do so. For example, it is by no means settled how or by what pathways visceral pain is mediated to the central nervous system. There is a difference of opinion concerning whether a pathologic viscus sends pain impulses to the central nervous system by way of visceral afferent nerve fibers, whether the whole mechanism is one of referred pain, with the pain impulses traveling strictly the somatic afferent fibers, or whether a combination of direct and referred pain obtains.

The theories concerning visceral pain have been adequately reviewed by White² and by van Bogaert and Verbrugge³. These authors have presented excellent bibliographies.

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1 Stokes, J. H. *Modern Clinical Syphilology*, Philadelphia, W. B. Saunders Company, 1934, p. 1203.

2 White, J. C. *The Autonomic Nervous System: Anatomy, Physiology, and Surgical Treatment*, New York, The Macmillan Company, 1935.

3 van Bogaert, L., and Verbrugge, J. *The Pathogenesis and the Surgical Treatment of Gastric Crisis of Tabes. Neurorhamsectomy*, Surg. Gynec. & Obst. 47: 543-553, 1928.

However, it is generally agreed that in the case of gastric crises or of any of the forms of pain associated with tabes the lesion involves the roots of corresponding nerves. This simplifies the surgical problem to some extent. Nevertheless, it is still unknown whether such a lesion (with respect to pain) involves visceral or somatic afferent nerve fibers or both and, in the case of visceral afferent fibers, what the remote implications with regard to the visceral nervous system may be.

In this connection it is interesting to note that the "posterior column losses" were minimal in our patients. It would appear that when locomotor ataxia supervenes, indicating an advanced deafferentation, the lesion itself will have destroyed the pain-bearing fibers.

Because of the vagal phenomena (nausea and vomiting) often associated with gastric crisis, it has been felt that the lesion involves the roots of the vagus nerve (Foerster⁴) or that the vagus nerve plays some primary or independent role (Oldberg⁵). Oldberg, in reference to chordotomy, stated "There are certain things one must not expect this operation to do—one is to relieve the vomiting which is so often associated with gastric crisis of tabes dorsalis. This vomiting is vagal in character and so, of course, would not be affected by a spinal cord operation." This expresses, undoubtedly, a rather general feeling, but the chordotomies in our cases eliminated both pain and vomiting.

Van Bogaert and Verbrugge³ stated that as far as vagal crises are concerned subdiaphragmatic vagotomy is ineffective and section of the roots of the vagus nerve as proposed by Foerster⁴ has not been done sufficiently often to permit one to pass judgment on its merits. In 1 of their cases of the vagal type of crisis, amelioration obtained by section of the thoracic roots was so remarkable that for the time being they have decided to discard the various operations on the vagus nerve.

In addition to insisting on differentiation between splanchnic and vagal crises, Foerster⁴ has suggested the importance of the phrenic nerve in certain cases. He concluded that disease of the phrenic nerve causes a special type of crisis, characterized by pain in the shoulder, hyperalgesia of the neck and hiccup. Foerster would utilize the radiculospinal operation for the splanchnic form of crisis and section of the roots of the vagus nerve for the vagal forms.

We feel that the outstanding vagal reactions have been misleading. In all probability the nausea and vomiting associated with gastric crisis are a secondary phenomenon and reflex to the primary stimulus. If impulses from the primary stimulus are eliminated, the vomiting should

4 Foerster, D. Foerster'sche Operation (No 7). Discussion über den Vortrage des Herrn Kuettner, Verhandl. d. deutsch. Gesellsch. f. Chir., 1910, pt 1, pp 29-31 and 42-46.

5 Oldberg, E. Chordotomy for Relief of Pain, S. Clin. North America 12: 1315-1322, 1932.

cease also. It is unnecessary to assume that the vagus nerve is primarily involved by the lesion in order to explain the associated reactions. Severe stimuli to the vestibular end organ cause nystagmus, dizziness, past pointing and vomiting, but one would not ascribe the nystagmus to a lesion of a direct stimulus of the third, fourth and sixth nerves or the vomiting to a direct stimulus of the vagus nerve. These reactions are integrated responses to the vestibular stimulus, and all are eliminated by section of the vestibular nerve. We feel that the vomiting associated with gastric crisis is in the same sense a reflex response to a severe stimulus of splanchnic afferent nerve fibers, the stimulus occurring at the spinal roots. The mechanism is subserved by the vagus nerve, but if impulses from the primary stimulus were eliminated, this particular reflex mechanism of vomiting would also be eliminated. This procedure would not stop vomiting that is reflex to other stimuli. Frazier⁶ has touched on this problem, with much the same conclusions.

Foerster called attention to the important role of the posterior roots in the mechanism of gastric crisis, but posterior radicotomy of even a large number of roots has not been uniformly successful. In opposition to the Bell-Magendie law, he defended the concept that anterior roots conduct certain types of sensibility and stated that in 1911 he began to resect the anterior roots. However, after cutting posterior and anterior roots and even the spinothalamic tracts, Foerster concluded that the pain must take some other route than that which he eliminated. He stated "One must think of the possibility of pain stimuli being conducted from the stomach by way of the periarterial sympathetic plexus of the gastric vessels, the aortic plexus, the sympathetic trunk, and from there to the cord by the corresponding rami communicantes (eighth cervical to third lumbar roots)."

We feel that herein lies the crux of the problem, that the rhizotomy (of posterior roots) has not been carried high enough.⁷ Certainly chordotomies below the third dorsal segment have not been uniformly successful, but in our 8 cases bilateral chordotomy above the third dorsal segment has resulted in complete cure, and there has as yet been no return of pain in any of the cases. Thus, it may well be that some splanchnic afferent fibers course upward in the sympathetic chain to enter the cord at least as high as the third dorsal segment and if rhizotomy were carried to that level it might be uniformly effective. For this operation to be complete, however, it would be necessary to

⁶ Frazier, C. H. *Surgery of the Spine and Spinal Cord*, New York: D. Appleton and Company, 1918, p. 702.

⁷ Frazier,⁶ in explaining the failures of rhizotomy, suggested the possibility that some afferent sympathetic fibers from the stomach may enter the cord at a level higher than the fifth thoracic segment.

cut the roots from the third dorsal to the twelfth dorsal inclusive and possibly to the second lumbar

The method of neuroramisectomy (technic of von Gaza) has been used by van Bogaert and Verbrugge.³ It consists of extraspinal section of about the sixth to the tenth spinal nerve, including section of the rami communicantes to these nerves. If the lesion is in the posterior roots, it is difficult to see how this operation can be effective. All visceral and somatic afferent fibers are severed distal to their cell bodies as well as distal to the lesion. Three cases are reported. In the first case, the seventh to tenth dorsal nerves with their rami were severed on the right. The patient seemed better and was relieved of pain, but died in three weeks of cachexia. In the second case, the seventh to eleventh dorsal nerves and their rami were severed on the right. After three months the crises returned. The fifth and sixth nerves on the right were severed, resulting in cure for more than a year. In the third case, the sixth to tenth dorsal nerves and their rami were severed on the left. Six months after operation the pain remained suppressed on the left, but not entirely on the right, and the mild gastric disturbances were not improved.

Frazier⁶ summed up the situation to 1918 by listing the operations which are directed at peripheral nerves and those which result in degeneration of posterior roots. Among the former he discussed stretching of the solar plexus (Jaboulay, 1900). (The technic of von Gaza should be included here.) Among the latter he discussed the following methods: 1. Extraction of the peripheral nerves with their ganglia. This operation has been associated with a high morbidity and mortality, and its effectiveness depends on destruction of the posterior roots. 2. Extradural ganglionectomy (Sicard and Desmarest, 1912). This should be applicable only to lesions of the thoracic region. At the time of Frazier's report the operation had not been given sufficient trial. 3. Extradural rhizotomy (Guleke, 1910). This does not differ in effect from intradural section of posterior roots except that it unnecessarily includes anterior roots. 4. Ligation of both anterior and posterior roots (Sauve and Tinel, 1913). 5. Intradural rhizotomy (Foerster, 1909). This has been discussed previously. It was endorsed by Frazier as the most logical procedure. Frazier stated that the sensory sympathetic supply of the gastrointestinal tract includes positively the fifth to twelfth thoracic nerves and possibly the first and second lumbar nerves. Although in most cases crises originate between the level of the seventh and that of the ninth thoracic segment, many patients are not relieved by section restricted to this region. The results of Foerster's rhizotomy, based on 73 cases in the literature, are expressed as follows: 2 in 10 patients cured, 4 in 10 improved, 1 in 10 unimproved, 1 in 10 dead and the remainder not clearly reported on or dead soon thereafter.

Frazier did not condemn chordotomy, but by 1918 there had not been sufficient experience with this procedure to warrant conclusions. Kahn and Barney⁸ reported the case of a patient in whom a bilateral chordotomy was done at the level of the fifth thoracic segment. The level of loss of pain was at the umbilicus, and the crises were not relieved. The splanchnic nerves were sectioned, and later the ramus communicans of the eleventh and twelfth thoracic nerves. The pain still being unrelieved, a bilateral chordotomy was done at the seventh cervical segment and was followed by complete relief.

Mixter and White⁹ reported the case of a patient who had severe pains in the left lower ribs and in the left side of the abdomen for four years. He was addicted to the use of morphine and had had three previous operations. Bilateral chordotomy failed, but the operation was not complete, as was shown by sensory examination. Section of the posterior roots from the fifth to the tenth dorsal inclusive gave no relief. Removal of the seventh to the ninth sympathetic ganglion gave relief from the pains in the left side of the abdomen. Lastly, ramisection from the fourth to the seventh dorsal segment inclusive gave relief from the thoracic pain.

White² (page 288) reported the case of a patient in whom portions of the right major and minor splanchnic nerves were resected beneath the diaphragm. The patient was relieved of severe pain in the right upper quadrant of the abdomen for two months, but the pains shifted to the right lower quadrant. It was necessary to perform a chordotomy to obtain complete relief. White stated that in the future he intended to utilize von Gaza's ramisection or injection of alcohol and procaine hydrochloride into the thoracic ramus as the therapy of choice for gastric crises. He had concluded that section of the spinothalamic tract should be reserved for patients who fail to obtain relief with other operations or for patients with widespread involvement of the lower extremities.

Platou and Sathre¹⁰ reported a case of gastric crisis in which complete cure to the time of writing (twelve months) was obtained after bilateral chordotomy at about the second and third dorsal segments.

8 Kahn, E. A., and Barney, B. T. Anterolateral Chordotomy for Intractable Pain of Tabes Dorsalis, *Arch Neurol & Psychiat* **38** 467-472 (Sept.) 1937.

9 Mixter, W. J., and White, I. C. Pain Pathways in the Sympathetic Nervous System. Clinical Evidence. *Arch Neurol & Psychiat* **25** 986-997 (May) 1931.

10 Platou, E., and Sathre, H. Chordotomie (Durchtrennung der Schmerzhahnen im Rückenmark) bei Tabes dorsalis. *Acta clin Scandinav* **75** 256-272 1934.

So far as we can ascertain, Benedek and Hutt¹¹ are the only authors who have expressed definitely the belief that chordotomy is an ineffective and dangerous treatment for gastric crises. After an experience with 3 cases they endorsed conservative therapy and stated that they would turn to chordotomy only as a last resort. In their first case the crises returned after a month. The patient in the second died after the operation, and the patient in the third acquired pains in the legs after the operation.

We would, of course, advise that conservative therapy be given a trial and certainly that the syphilis be given adequate treatment before an operation is considered. However, it should be borne in mind that such drastic therapy as the malaria treatment will often have a severe influence on a patient who already is in a poor state of health. This treatment gave practically no benefit in our cases, and in certain instances it had to be terminated because of untoward reactions. Conservative therapy can at times be more radical than certain forms of operative therapy.

We are reporting 8 cases of gastric crisis treated by anterior chordotomy. The first case is reported somewhat in detail in order to demonstrate the motor and sensory effects of complete section of the anterior quadrants of the cord. Cases 2 and 3 have been reported in a previous communication.¹²

REPORT OF CASES

CASE 1—J. J., a white man aged 38, was referred to the department of neurology on June 16, 1937, by Dr. Robert Netolicky, of Cedar Rapids, Iowa.

Since 1935 he had suffered severe spells of vomiting accompanied by acute abdominal pain. At first these attacks occurred every six months. They had progressed in frequency since January 1937, there being at least one attack every month. Not only the attacks but the fear of them had broken the patient's morale and had caused a loss of 35 pounds (16 Kg.) in weight in the past ten months.

In 1935 it was found that he had a positive Wassermann reaction. Antisyphilitic therapy, consisting of forty intravenous and thirty intramuscular injections, was given. The patient had no knowledge of a primary lesion.

Past History—He had been in good health until 1935. Appendectomy and an operation on the gallbladder were performed in that year.

Examination—The patient was dejected and badly nourished. Although Argyll Robertson pupils were present, the neurologic examination otherwise gave essentially negative results. There was no clinically demonstrable involvement of the posterior columns.

Laboratory Data—The value for hemoglobin was 14 Gm. per hundred cubic centimeters of blood. There were 5,300,000 erythrocytes and 5,700 leukocytes per

¹¹ Benedek, L., and Hutt, T. "Ueber den Wert der Chordotomie bei 'Crise gastrique,'" *Beitr. z. klin. Chir.* **161**: 621-644, 1935.

¹² Hyndman, O. R., and Van Epps, C. "Possibility of Differential Section of the Spinothalamic Tract. A Clinical and Histologic Study," *Arch. Surg.* **38**: 1036-1053 (June) 1939.

cubic millimeter of blood The smear was normal The urine was normal The Wassermann reaction of the blood was 4 plus The pressure of the spinal fluid was 110 mm of water with the patient in the prone position There were 200 lymphocytes per cubic millimeter The reaction for globulin was 3 plus, the gold curve 1122200000 and the Wassermann reaction 3 plus

Treatment and Course—The patient was inoculated with malarial blood Eight days later he had the first chill He was permitted to have only six chills, because his condition became poor The attacks of abdominal pain became frequent necessitating numerous hypodermic injections of morphine These, as well as administration of chloral hydrate, sodium bromide and sodium amytal (intravenously, 15 grains [0.97 Gm.] daily) gave only fair relief Section of the spinothalamic tracts was advised, and the patient was transferred to the surgical service During the succeeding five days he had daily attacks of severe gastric crises These consisted of repeated vomiting, hard retching, excruciating pain and profuse sweating He stated that it felt as though his abdomen were being squeezed in a vise He was able to take and retain very little nourishment He appeared pale and exhausted, and the level of hemoglobin had fallen to 12 Gm He became so despondent that he attempted to strangle himself with a cord tied to the side of the bed

Examination—An attempt was made to obtain as definite a clinical impression as possible of the sensory and motor status and the muscular tone The following findings represent the consensus of three examiners

Motor Status The calf muscles were normal to palpation The heel to and ankles was normal The calf muscles were well performed Alternate movements of the knee and the toe to finger test were well performed The heel to the legs were well performed Station was maintained well with the eyes closed and the heels together The patient hopped well on one foot, walked a straight line well and turned without faltering The reflexes were as follows

Right	Biceps	Knee	Achilles	Plantar	Abdominal
Left	2+	Jerk	Tendon	Flexion	0
	2+	2+	1+	Flexion	0
		2+	1+		

Sensory Status	The following data were obtained	Shins	Hands
Pain		100 per cent	100 per cent
Cotton		100 per cent	100 per cent
Heat		100 per cent	100 per cent
Pallesthesia		100 per cent	100 per cent
Two point discrimination		100 per cent	100 per cent
Sense of position		8 cm	5 cm
		Good	Good

The soles were normally ticklish There was an area of hyperesthesia corresponding to the segments from the ninth dorsal to the first lumbar

Operation—The second, third and fourth dorsal laminar arches were removed The third posterior root on each side was sectioned In order to assure complete abolition of pain, a cataract knife was inserted deeply, as shown in figure 1, and the point was brought out at the anteromedian fissure The same procedure was carried out on the opposite side at a slightly different level Some bleeding was encountered but was easily controlled with cotton pledgets and warm saline solution

The operator (O H) is convinced that he sectioned the entire anterior half of the cord and consequently all of the descending extrapyramidal tracts except possibly the posteriorly placed rubrospinal tracts

Course—The patient made an uneventful recovery. All the symptoms related to the gastric crises, including pain and vomiting, have been completely abolished to the time of writing (twenty-five months)

Discrimination of pain and temperature was abolished from the fifth dorsal segment down, although sensitivity to light touch, pressure and vibration, two point discrimination and sense of position were not essentially impaired at any time

For about ten days the patient complained of "girdle pain" in the third dorsal segment, but the pain (as well as a degree of hyperesthesia) was limited to this segment

For five days (including the day of operation) he was unable to move his legs. On the sixth day voluntary function began to return and progressed gradually to 100 per cent recovery. During the five day period the paraplegia was flaccid, with complete absence of all reflexes, including the flexion reflexes. On the seventh day the knee jerks were 1+ bilaterally, and they developed gradually to 2+ by

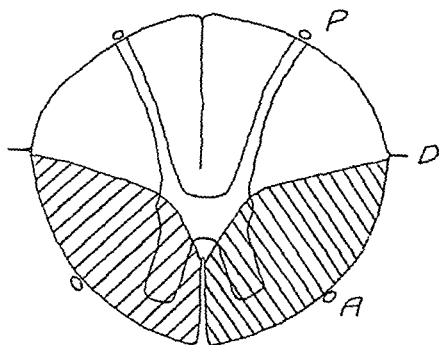


Fig 1—Diagram illustrating the manner in which the cord was sectioned in case 1. *P* indicates posterior root, *D*, dentate ligament, *A*, line of anterior roots

the twenty-fourth day. The achilles tendon jerks made their feeble appearance several days after the appearance of the knee jerks and developed to 1+ bilaterally by the twenty-fourth day. Response to plantar stimulation appeared after the return of the ankle jerks and was present to a normal degree by the twenty-fourth day.

Since the operation there has never been the slightest semblance of so-called upper motor neuron signs—extensor spasticity, hyperactive deep reflexes, dorsal flexion of the great toe, or ankle or patellar clonus.

Voluntary control of the bowels and bladder was lost for about sixteen days and then gradually returned to normal.

The patient felt most grateful for the relief from his crises. His interest in life and his ambition returned, and when he realized that he could retain food his appetite increased rapidly.

One month after the operation the flexor and extensor strength of his legs was 100 per cent. During recovery there was never the slightest evidence of *asynergy*, *ataxia*, incoordination or tremor. The heel to knee and the toe to finger test were normally performed. In short, when motor movement became possible, there was never any disturbance in the pattern.

Caloric tests were done prior to operation, and, although myasthenia and past pointing of the upper extremities were normal, for some reason there was no past pointing of the lower extremities, and consequently this study failed to attain its intended significance postoperatively.

It was obvious on palpation that the muscles of the thighs and calves were soft, flabby and without tone. At the time the patient was discharged (the twenty-ninth postoperative day) he was walking and performing in all respects with normal movement pattern but was easily fatigued. A walk of twenty steps would cause him to perspire from fatigue. Motion pictures were taken as a record of his gait.

Follow-up Examination—Six months after the operation a follow-up examination revealed the patient to be healthy appearing, contented, ambitious and grateful, with no complaints. He had been working full time at his trade carpentry and mechanics. He worked on and around scaffolding with ease. He had gained 25 pounds (11.5 Kg.) since his operation. He slept well. He had full control of the bowels and bladder.

Motor Status The neurologists who examined the patient, Dr. Clarence Van Epps and Dr. C. G. Barer, stated that they were unable to elicit a single motor abnormality of the lower extremities. Station, gait, hopping and running were normal and were accompanied by no more than ordinary fatigue. Alternate movements of the lower extremities were normal. There was no evidence of ataxia, ataxia or incoordination. The reflexes were as follows:

	Biceps	Knee Jerks	Achilles Tendon	Plantar
Right	2+	2+	1+	Flexion
Left	2+	2+	1+	Flexion

The thigh and calf muscles were normally firm and solid to palpation, and the patient could hold his leg suspended from the table exceptionally well without becoming fatigued.

Sensory Status There was loss of appreciation of pain and temperature from the fifth dorsal segment down.

The cutaneous reactions of the shins to various tests and stimuli were as follows:

Pain	0
Cotton	100 per cent
Heat	0
Pallesthesia	100 per cent
Two point discrimination	8 cm
Sense of position	Good

At present the lower extremities feel comfortable and are never numb. There is a mild sensation of warmth. The patient can sense accurately when the hairs of his legs are pulled, but the sensation is unaccompanied by pain. He states that a pin scratch feels like the dragging of a blunt stick across his skin. The soles continue to be as ticklish as they were prior to chordotomy. He senses accurately breath blown on his lower extremities but cannot discriminate its temperature. He cannot appreciate the presence of water on his legs and once he was unaware that his trousers were soaking wet. The psychic power of erection is completely lost, and, though a moderate desire for intercourse remains, the act is impossible. On occasions, however, in the morning before the bladder is emptied he has noticed an erection.

He has remained well to the time of writing (two years).

CASE 2—L K, a white man aged 56, was referred by Dr Charles Dimond, of Keokuk, Iowa, on June 8, 1937

He complained of severe attacks of abdominal pain and vomiting for the past three years, loss of 15 pounds (7 Kg) in weight in the past six months and difficulty in voiding urine for ten years. The abdominal crises consisted of sharp attacks of colicky pain referred to the epigastrium. The attacks were accompanied by vomiting and retching but were unassociated with meals. They often occurred on several successive days. They occurred at least once a week and were relieved only by hypodermic injections of morphine.

He contracted syphilis in 1913 and stated that he had had one hundred injections, intravenous and intramuscular, since that time.

Examination—The positive findings on neurologic examination were absence of the pupillary reaction to light and in accommodation, weak knee jerks on reinforcement, absence of the right ankle jerk on reinforcement, and slight swaying with the heels together and the eyes closed.

Laboratory Data—The blood and urine were normal. The spinal fluid contained 16 lymphocytes per cubic millimeter and 40 mg of protein per hundred cubic centimeters. The Wassermann and Kahn reactions were positive on one occasion and negative on two.

Treatment—The patient was given malaria therapy, but the blood pressure dropped so low with the fifth chill that the treatment was terminated. He then received courses of neoarsphenamine, a bismuth compound and tryparsamide. During the treatment he had a gastric crisis lasting six days.

He was discharged in August with instructions to continue treatment and progressed satisfactorily until December, when the crises returned with their previous severity. From this time on he had a continuous girdle-like sensation about the waist and continued to lose weight.

He returned to the hospital on March 20, 1938.

Operation—On March 26 the second, third and fourth dorsal arches were removed, and a bilateral chordotomy was performed in the region of the third segment. The right spinothalamic tract was completely sectioned, on the left a superficial anterior section was made so as to eliminate pain in the chest and abdomen without involving that in the leg.¹³

Function of the bladder was regained on the day after the operation, and motor function of the lower extremities was not impaired.

Result—The patient has been free of both pain and vomiting to the time of writing (sixteen months).¹⁴

¹³ Differential section of the spinothalamic tract has been discussed in a previous paper,¹² in which the case of this patient was reported, with diagrams illustrating the pattern of the section and the sensory changes.

¹⁴ At the time the proof of this paper was read the patient had returned to the hospital complaining of a recurrence of the crises. On Nov 13, 1939, the analgesia over the right side of the chest was found to have practically disappeared. Anterior chordotomy was repeated, the section being made between the fifth and the sixth cervical segment on the left and between the sixth and the seventh cervical segment on the right. Sensibility to pain and temperature was lost to the level of the third dorsal segment bilaterally. The patient recovered uneventfully, and crises have been abolished to the time of writing (two months).

This case teaches that unilateral chordotomy will not abolish gastric crises. While differential chordotomy is a possibility, it is not wise to attempt less than a complete section of the spinothalamic tracts in the treatment of gastric crises.

CASE 3—C K, a white man aged 27, was referred in April 1938 by Dr C M Wray, of Iowa Falls, Iowa

Three years previously his illness had begun with attacks of nausea and vomiting associated with very little pain. They occurred at least once a month. After a year, sharp, nonradiating epigastric pain was associated with the attacks, and the frequency increased so that he had an attack at least each week. As a rule the attacks lasted several days, occasionally they lasted as long as ten days. In contradistinction to most of the other cases in this series, the nausea and vomiting appeared to be more severe than the pain.

In June 1937 a gastroenterostomy had been performed, after a diagnosis of peptic ulcer. The Wassermann reaction was later found to be 4 plus, and he was given sixty-four intravenous and sixty-four intramuscular injections.

In the past few months he had wet the bed on several occasions.

He had lost weight steadily during the past three years.

During his stay in the hospital before operation (one month) he seldom had a two day period free of pain and vomiting. During the attacks, which would last usually a day and a night or two days, it was necessary to stop administration of anything by mouth and to give chloral hydrate by rectum and fluid by vein.

Examination—It was striking that the usual signs of tabes were minimal. The pupils were normal. The deep reflexes were absent. Sensation was well preserved except for some diminution of two point discrimination and sense of position in the lower extremities. There was slight swaying with the heels together and the eyes closed.

The Wassermann reaction of the spinal fluid was 4 plus.

Roentgen examination after administration of a barium sulfate meal revealed a functioning gastroenterostomy opening and an otherwise normal stomach.

Operation—On May 5 the first, second and third dorsal laminar arches were removed and bilateral chordotomy was carried out with the region under local anesthesia. (This case was reported in a previous paper,¹² in which are given diagrams to illustrate the manner in which the cord was sectioned and the results of sensory examination.) On the right a complete section of the anterior quadrant was made from the dentate ligament to the anterior median fissure. On the left the section was begun at a point halfway between the dentate ligament and the anterior root and carried to the anterior median fissure.

Result—Recovery was uneventful except for retention of urine requiring catheterization for two weeks. The patient voided occasionally during this period but retained some residual urine. He was voiding well when discharged, three weeks after the operation.

Pain and temperature sensibility were lost to the nipple line, but there were no demonstrable changes in other forms of sensation by routine tests. Motor function in the lower extremities was weak for several days but rapidly returned to normal before the patient's discharge.

There was no semblance of an attack while the patient was in the hospital.

A check-up examination four months later revealed no subsequent changes in the sensorium. The patient's strength was normal, and he had gained 20 pounds (9 Kg). He had no difficulty in voiding urine. Since leaving the hospital he had had four brief attacks of vomiting without pain. He was happy over the result and has remained well to the time of writing (fifteen months).

CASE 4—R R, a white man aged 28, was referred by Dr A J Meythaler, of Earlville, Iowa, on Sept 16, 1938.

He complained of severe abdominal pain and vomiting of one month's duration. On August 28 he was suddenly seized with a severe, knifelike epigastric pain which radiated to the umbilicus, and he immediately began to vomit. The pain had continued almost without interruption until his admission, except for periods of relief from hypodermic injections of morphine sulfate (four to six daily). Vomiting was extreme. There were periods of intractable hiccups. He had no desire for food, and the sight or smell of it brought on severe nausea and retching. During several days prior to his admission the pain and vomiting had gradually lessened, and these symptoms were slight when he reached the hospital. After five days in the hospital they subsided completely, and he left, spurning treatment, against the advice of the staff. Six days later the pain and vomiting suddenly began again and grew steadily worse. He reentered the hospital on October 5, anxious to accept any therapy for relief.

In 1930 the patient had had a penile lesion. In February the Wassermann reaction had been 4 plus and he had been treated by intravenous and intramuscular injections until September. There had been no other manifestation of tabes. He had suffered from perennial asthma for years.

Examination—When first seen the patient was doubled up, in the knee-chest position, pressing his fists into his abdomen and retching and vomiting constantly. He was acutely ill, with evidence of marked loss of weight. The right pupil was dilated and the left irregular. The pupils reacted in accommodation but not to light. Except for lessened activity of the patellar reflexes there was no evidence of neurosyphilis. Sibilant rales and rhonchi were heard over both lung fields. The abdominal muscles were voluntarily spastic, and there was slight epigastric tenderness. There was a penile scar.

Laboratory Data—The value for hemoglobin was 90 per cent. There were 4,500,000 erythrocytes and 4,600 leukocytes per cubic millimeter of blood. The Wassermann reaction of the blood was 4 plus. The spinal fluid was clear, it gave a negative reaction for globulin and a negative Meyers reaction. The spinal fluid pressure was normal. The fluid contained no cells. The Wassermann reaction was positive. The concentration of total protein was 50 mg per hundred cubic centimeters.

Operation—On October 12 an anterolateral chordotomy was performed at the level of the second and third thoracic segments. Immediately after section of the anterior columns, pain and temperature senses were lost to the axillary level.

For forty-eight hours after the operation there were complete motor paralysis of the lower extremities and complete retention of urine. Motor function slowly returned, and when he left the hospital, on the twenty-fifth postoperative day, he was able to walk and function of the bladder had returned.

From the operation to the present time (nine months) he has not vomited. His pain was immediately and completely relieved and has not recurred. His appetite is good, and he has gained 10 pounds (4.5 Kg). There is low grade cystitis which causes frequency of urination. He is most happy with the result.

CASE 5—J. L., a white man aged 56, was referred by Dr. John T. Hecker, of Cedar Rapids, Iowa, on Sept. 30, 1938, with complaints of severe abdominal pain, nausea, vomiting and loss of weight for six years.

In July 1932 he was suddenly seized with severe, gripping pain over the entire abdomen, and he vomited in projectile fashion. This occurred almost daily until December 1932, when a stoneless gallbladder was removed. After the operation, while still in the hospital, he had an identical attack, this prompted his first Wassermann test, which elicited a positive reaction. During the subsequent intensive

antisyphilitic treatment he had no further attacks. Identical episodes began again in 1935, recurring at short intervals. For three months prior to his admission he had scarcely been free of pain for a day, had taken daily hypodermic injections of morphine sulfate and had lost 18 pounds (8.2 Kg). The pain and vomiting became more and more severe.

Gonorrhea was contracted in 1899, but syphilis had not been suspected.

Examination—The patient was cachectic and pallid. He presented no positive neurologic abnormality other than irregularity of the left pupil, bilaterally poor pupillary reaction to light and reduction of pallesthetic sense over both tibias.

Laboratory Data—The blood and the urine were normal. The Wassermann reactions of both the blood and the spinal fluid were negative. The result of the Kahn test was equivocal. The spinal fluid contained 15 lymphocytes per cubic millimeter. It gave a negative reaction for globulin. The value for total protein was 37 mg per hundred cubic centimeters.

Röntgen examination of the stomach and of the duodenal bulb showed no lesion.

Operation—On October 17 an intercostal chordotomy was performed at the level of the second and third thoracic segments, with the region under local anesthesia. Pain and temperature senses were immediately lost to the nipple line. There was transient paralysis of both legs for forty-eight hours after the operation, with the usual brief period of retention of urine. There was no further abdominal pain or vomiting. The patient left the hospital on the eleventh postoperative day, ambulant and satisfied with the result.

He gained weight and strength and was planning to return to work, but on November 8 he died suddenly, with cerebral hemorrhage suspected as the cause.

CASE 6—A R., a white man aged 49, was referred by Dr. F. N. Cole, of Iowa Falls, Iowa, in February 1939.

He had been treated in this hospital off and on since 1935. His complaints at that time were dribbling of urine, shooting pains in the legs, failing vision and crawling sensations in the hands and feet. He was given routine antisyphilitic treatment and a course of malaria in 1937. He was improved for a time, but the shooting pains in the legs returned, and in December 1938 he had girdle pains associated with nausea and vomiting. On his present admission to the hospital these crises were occurring daily, and food was difficult to take and retain. He had lost 15 pounds (6.8 Kg) in the past two months.

Examination—The significant findings were irregular and unequal pupils with a sluggish reaction to light. The deep reflexes were obtained on reinforcement. There was absence of sensation to pain over the shins. The station and gait were normal.

Laboratory Data—There was mild secondary anemia. The urine was normal. The spinal fluid contained 57 lymphocytes per cubic millimeter. The Wassermann reaction was 3 plus. The pressure was normal.

Operation—On February 8 the upper three dorsal laminae were removed with the region under local anesthesia. The cord appeared smaller than normal, and the arachnoid was somewhat thickened. Bilateral incisions were made into the cord, beginning about 2 mm anterior to the dentate ligament and emerging about 3 mm mesial to the anterior roots and being 2.5 to 3 mm deep. The levels of the incisions were separated by about 2 cm. The patient was tested and found to have lost sensibility to pain to the nipple line.

Course—Save for a transient infection of the upper respiratory tract the patient made an uneventful recovery. He was discharged in ten days. He was incontinent

to about the same degree as before operation. Eight days later he returned because of cystitis, which responded well to the usual management. He has since remained in good health and completely relieved of the crises (five months).

CASE 7—A man aged 65, a physician, complained of pain from gastric crises of eight months' duration.

He had contracted syphilis in 1897, but after treatment with mercury compounds and iodides he was free of symptoms until 1912. He then had photophobia and visual difficulties. Changes in the pupils were disclosed, and the Wassermann reaction was positive. After treatment with arsphenamine and later with neoarsphenamine and bismuth preparations the Wassermann reaction of the blood became negative and remained so. He had "lightning pains" in the legs in 1919, these became so severe that he was compelled to quit his practice in 1937. The gastric crises began eight months ago. The attacks consisted of severe epigastric pain without radiation and were always accompanied by nausea and vomiting. There had been as many as eight attacks in twenty-four hours. He had taken morphine sulfate and dilaudid hydrochloride in increasing doses, so that when examined he alternated between $\frac{3}{8}$ grain (24 mg.) of the former and $\frac{1}{16}$ grain (4 mg.) of the latter every two hours.

Examination—The positive findings were unequal, enlarged pupils reacting very slightly to light, absence of knee and ankle jerks, a slightly ataxic gait, and diminished sensation to pinprick over the shins. Ability to void was diminished, and there was about 100 cc. of residual urine.

Laboratory Data—Routine examinations of the blood and urine gave essentially negative results. The Wassermann reactions of the blood and spinal fluid were negative.

Operation—On March 28, 1939, the upper three dorsal laminar arches were removed. The second posterior thoracic root was sectioned on each side, and bilateral chordotomy was performed in the same manner as in case 6. Cutaneous sensibility to pain and to temperature was lost to the nipple line.

Course—The postoperative course from a surgical standpoint was uneventful, but the problem of withdrawal of narcotics had to be met with the greatest patience. The morphine and dilaudid were gradually replaced by codeine over a period of ten days and at the time of his discharge, twenty-five days after the operation, he was receiving only 1 grain (0.06 Gm.) of codeine sulfate every three hours. During the withdrawal of morphine he complained of vague pains in the legs, bladder and rectum. The origin of these pains must undoubtedly have been central. There was the usual postoperative retention of urine. He regained the ability to void urine before leaving the hospital but carried about 300 cc. of residual urine. The gastric crisis syndrome (pain and vomiting) did not reappear. The strict withdrawal of narcotics, however, was poorly tolerated, and he died of circulatory failure two months later, after a ten day period of delirium.

CASE 8—A R., a white man aged 33, had had lightning pains in the legs beginning two years prior to examination. Shortly thereafter he began having attacks of pain in the chest. The pain was located in the epigastrium and did not radiate. He had a sense of constriction as if a band were being tightened about the lower part of the chest. Vomiting and retching with the attacks were marked. He stated that he had vomited as many as forty times in one day, and he felt that the vomiting was worse than the pain. The attacks occurred at intervals of about two months and continued for three to four weeks. He had acquired an aversion

to food and during the attacks could not keep even a teaspoonful of water on his stomach. There had been some dribbling of urine and also difficulty in starting the urinary stream.

Examination—The positive findings were Argyll Robertson pupils, knee and ankle jerks present only on reinforcement, a positive Romberg sign, and delayed pain sensation over the shins. There was hydronephrosis on the left.

Laboratory Data—Moderate anemia following malarial treatment was present. There were 3,830,000 red cells per cubic millimeter of blood. The urine was essentially normal except for many red cells at times. The Wassermann reaction of the blood was positive.

Spinal Fluid—Dynamic and cytologic tests gave negative results. The Wassermann reaction of the spinal fluid was doubtful.

Treatment—The usual antisyphilitic therapy was given. Malaria was induced, and four severe chills were allowed to occur. It was the impression that the malaria initiated an attack of gastric crisis which persisted for two weeks.

Operation—On April 25 a bilateral chordotomy was done (with the use of local anesthesia) at the second and third dorsal segments, as in the previous case.

Course—Cutaneous sensibility to pain and temperature discrimination were lost to the seventh rib on the right and to the nipple on the left. Ability to void returned in nine days, but dribbling continued the same as before operation. His course was uneventful, and he was discharged, walking normally, on the sixteenth day. The gastric crises, including pain and vomiting, have not reappeared to the time of writing (three months).

COMMENT

In our 8 cases the results were gratifying to the patients and to us. These are the only patients for whom we have attempted surgical treatment thus far. We feel that chordotomy guarantees relief from crises, but certain demands must be fulfilled. The chordotomy should be bilateral and should be carried out preferably at the second dorsal segment—not lower than the third. The spinothalamic tracts must be completely sectioned, the cutaneous level of loss of sensibility to pain being brought to the nipple line.

From an experience with sixty chordotomies, one of us (O. H.) feels that he has deduced the fact that spinothalamic tracts are farther anterior in the cord than is ordinarily believed. An incision 3 mm deep beginning 2 mm anterior to the dentate ligament and carried 3 mm mesial to the anterior root will section the tract completely at an upper dorsal level (fig 2). The 2 mm region anterior to the dentate ligament is "silent" so far as pain and temperature are concerned. Unless the section is carried beyond the anterior root the level of loss of sensibility to pain will not be at its maximum height and the section will not be complete.

There are disadvantages which must be accepted with bilateral chordotomy: loss of cutaneous sensibility to pain and temperature, retention of urine necessitating catheterization for ten days to two weeks, the possibility of serious consequences from any incision of

the cord (although none occurred in these cases), and the loss of sexual function (erection and orgasm) None of our patients appeared to regret the loss of sexual function One other patient, however, has refused the operation for this reason

We feel that the significant advantage of chordotomy in the treatment of intractable gastric crises is that it offers practically certain abolition of the pain and vomiting after one operation, an operation which requires a small laminectomy

A patient who has spent many hours over a vomiting basin, suffering agonizing and relentless pain, and who has come to dread the sight of food is in a desperate frame of mind It is striking to note how apprehensive the patients are for a few days after the operation lest ingestion of food bring on an attack When they are confident that the pain and vomiting have been eliminated, they show complete reha-

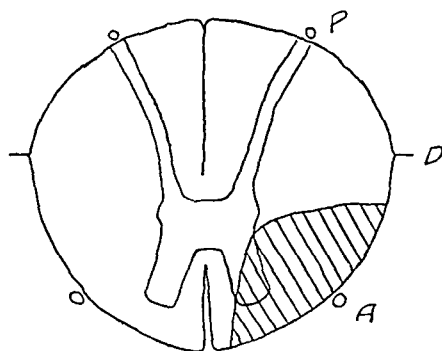


Fig 2—Diagram to illustrate the manner in which a section is made to include the entire spinothalamic tract at a high dorsal level *P* indicates posterior root, *D*, dentate ligament, *A*, line of anterior roots

bilitation of their mental outlook Their appetites improve greatly, the hemoglobin content of the blood increases and they gain weight All the patients in this series have been grateful and anxious to return to a gainful occupation

SUMMARY

Eight cases of gastric crises of tabes dorsalis are presented The patients were treated by bilateral chordotomy at the second and third dorsal segments In case 1 complete section of both anterior quadrants of the cord was made and careful studies of motor function carried out In case 2 the spinothalamic tract on the right was completely sectioned That on the left was partially sectioned in order to eliminate pain only in the chest and abdomen on that side In the remaining cases the spinothalamic tracts were sectioned completely on both sides

In case 5 the patient was free of pain and vomiting from the time of operation, October 17, until death on November 8, with cerebral

hemorrhage suspected as the cause. In case 7 the patient died from withdrawal of habitually used narcotics two months after the operation. The crises were eliminated during this period however. The other 6 patients have remained completely free of pain and vomiting to the time of writing (twenty-five, sixteen, fifteen, nine, five and three months respectively) with the exception of the patient in case 3, who has had short periods of vomiting on several occasions without pain. This patient had previously had a gastroenterostomy.

After the operation, function of the bladder was regained in sixteen, one, fourteen, seven, seven, ten, twenty and nine days respectively.

All the patients were walking alone when they left the hospital except 1 (case 7), who had not yet attempted to walk because of weakness from withdrawal of narcotics.

CONCLUSIONS

Complete bilateral section of the spinothalamic tracts above the third dorsal segment abolishes the pain and vomiting associated with the gastric crises of tabes.

Retention of urine and occasional motor weakness are transient sequelae. Loss of sexual function is permanent. Considering the beneficial results of this procedure, its disadvantages are minimal.

SEVENTY-FIRST REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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LOS ANGELES

CONGENITAL DEFORMITIES

Congenital Pseudarthrosis of the Tibia—Scott¹ briefly discusses the condition known as congenital pseudarthrosis of the tibia and presents a case in which the patient has been carefully followed from birth to the age of 4 years. He classifies patients with this type of deformity as follows: (1) those with well marked anterior angulation, with no fracture at birth, (2) those who show slight deformity at birth but in whom fracture and pseudarthrosis develop after slight trauma, (3) those who have had pseudarthrosis since birth, and (4) those who are normal at birth but in whom fracture and pseudarthrosis develop later. The author's patient, at birth presented marked angulation at the lower third of the tibia, with cyst formation higher in the bone. The cyst eventually healed and was followed by another cyst in a different place. There were typical sclerosis and narrowing of the medullary space in the lower half of the bone. In spite of careful protection with casts and braces, fracture finally occurred at the age of 2½ years and progressed to

This report of progress is compiled from a review of 120 articles selected from 152 titles dealing with orthopedic surgery which appeared in the medical literature approximately between Nov. 1, 1939 and March 1, 1940.

1 Scott, C. Am J Roentgenol **42** 104, 1939

pseudarthrosis The author feels that this condition is a form of congenital localized osteitis fibrosa cystica, with a poor blood supply at the point of fracture Little is known about its early development

[ED NOTE According to our experience, cyst formation is common but is not seen in every case]

Claw Foot—A study of 152 patients suffering from claw foot is presented by Hallgrímsson.² There were 58 male and 94 female patients Symptoms of this deformity commonly appeared between the ages of 11 and 20 years Fifty-three of these patients were given a careful neurologic examination Thirty-one had neurologic symptoms, and 21 had spina bifida The author did not believe that spina bifida and congenital myelodysplasia were of etiologic importance The data pointed to a slowly developing lesion of the central nervous system The exact nature of the nervous disorder was difficult to determine, since symptoms usually did not appear until adolescence Symptomatic treatment was commonly given The author favors transplantation of the peroneal tendons rather than cuneiform osteotomy About six months is required for the weight of the body to flatten and lengthen the arch of the foot

[ED NOTE The results of tendon transplantations for this deformity are discouraging Osteotomy when growth is almost complete is the most satisfactory treatment]

Fusion of the Cervical Portion of the Spine in Congenital Torticollis—Giutini³ reports 2 cases of congenital torticollis with fusion of the second and third cervical vertebrae This partial fusion induces a homologous deviation of the cervical portion of the spine Careful roentgen study in all cases of congenital torticollis will help in classification of such anomalies and is important for prognosis and cure A review of the literature is given

Late Results of Closed Reduction of Congenital Dislocation of the Hip—Deutschlander,⁴ of Hamburg, Germany, reports 4 cases of congenital dislocation of the hip in which the patients were followed for many years In the first the dislocation was reduced when the patient was 2 years old and was followed for twenty-eight years While there is no pain or functional disturbance referable to the dislocation, roentgenograms show extensive degenerative changes in the hip which cannot be differentiated from hypertrophic arthritis In the second case the patient underwent reduction of a congenital dislocation at the age of 3 years The appearance twenty-nine years later was that of marked

² Hallgrímsson, S Acta orthop Scandinav **10** 73, 1939

³ Giutini, L Chir d org di movimento **24** 519, 1939

⁴ Deutschlander, K Ztschr f Orthop **70** 38, 1939

deformity of the femoral head and of the acetabulum. In the other 2 cases the patients, with reduction performed at the ages of 2 and 3 years respectively, showed similar changes in the roentgenograms. Functional disturbances were not observed. At these ages, however, anatomic restoration of the hip probably does not occur, since this is a biologic deformity and not a true dislocation.

DEVELOPMENTAL DISEASES OF BONE

Marble Bones—Kramer and his associates⁵ made a chemical analysis of bone from an infant aged 4½ months with marble bones and rickets. They compared their findings with analyses made on the bones of an 18 week fetus, a 5½ hour infant, a 6 day infant, a 10 year old girl and a 29 year old man, none of whom had marble bones. They made determinations of the values for calcium, phosphorus, magnesium, carbon dioxide, water and fat. The percentages of ash, calcium and phosphorus were higher in the case of the infant with marble bones. The ratio of residual calcium to phosphorus was in harmony with the idea that the calcium-phosphorus compound in marble bones is tertiary calcium phosphate. They found a high carbonate content and hypermineralization. The high carbonate content was also present in adult and in rachitic bone and may account for the increased fragility. Hypermineralization is not associated with rickets. Hence the authors conclude that high carbonate content and hypermineralization characterize the mineral content of marble bones.

Madelung's Deformity—Thompson and Kalayjian⁶ present 4 cases of Madelung's deformity with photographs, line drawings and roentgenograms. This clinical entity, first described by Madelung in 1878, is a disturbance in growth, in most instances bilateral. It develops spontaneously, never before the age of 13 years and rarely after the age of 23. The authors state the belief that retardation of the rate of growth must precede premature closure of the growth plate of the radius if one is to account for the curvature in the diaphysis. Pain occurs only when the deformity is sufficient to distort or distract the distal radioulnar articulation. Premature closure of the radial epiphysal line of growth occurs, while the ulna continues to grow and projects dorsally and distally from the subluxated carpus and hand. The clinical symptoms consist of pain and limited motion in the carpus and the distal radioulnar articulation. The hand deviates to the ulnar side. The prominent distal end of the ulna may be replaced manually to the level of the wrist but returns to its dorsal position when pressure is released. Treatment,

⁵ Kramer, B., Yuska, H., and Steiner, M. M. Marble Bones. Chemical Analysis of Bone, *Am J Dis Child* **57** 1044 (May) 1939.

⁶ Thompson, C. F., and Kalayjian, B. *Surg, Gynec & Obst* **69** 221, 1939.

including epiphysial arrest and later resection of a portion of the diaphysis of the ulna near the wrist, was successful in obtaining a joint free from pain. Corrective osteotomies at the points of greatest curvature after completion of growth in both bones reduced the deformity and increased the function of the wrist and hand.

TUBERCULOSIS

Tuberculosis of the Knee in Childhood—McKeever⁷ discusses the treatment of tuberculosis of the knee joint in infancy and childhood. Forty-seven patients under 10 years of age with proved tuberculosis of the knee were studied to determine the results of conservative and of operative treatment. Surgical treatment was described as removal of articular cartilage to produce bony ankylosis between the tibia and the femur. All other procedures were considered conservative (traction, casts, braces, synovectomy, excochleation, sympathectomy and extra-articular fusion). Conservative treatment for one to nine years, an average of three years for 46 patients, did not result in any case in a knee which did not show clinical signs of active disease. One child was cured by excochleation of a tuberculous abscess in the tibial epiphysis. Two died under conservative treatment. Thirty-nine patients were subjected to "economical resection" aimed at producing femorotibial synostosis. Two died as a direct result of the operation. Thirty-four were followed, and 90 per cent were in excellent health. Thirty-three, 97 per cent, of the resected knee joints were solid clinically and roentgenographically, 3 patients required two operations, 2 required three operations and 1 required four operations before fusion was accomplished. A detailed account is given of disturbances of growth and directional aberrations in a follow-up which ranged from one and a half to thirteen years.

Tuberculosis of the Knee Joint—Toumey⁸ reports 222 cases of tuberculosis of the knee joint in which fusion of the knee was performed in the period from 1915 to 1936. One hundred and ninety-nine of the patients were followed from one to seventeen years after operation. Fusion occurred in 196, or 98 per cent. Fixation in plaster was stopped at an average of eight months after operation. The disease subsided in all but 7 patients, in whom sinuses persisted, and in no fused knee did tuberculosis recur. Fifty-nine patients were 10 years of age or less at the time of operation, and 14 were 5 years old or less. The diagnosis was made when flexion deformity, synovial thickening and marked atrophy of the thigh and calf were present, but it could not be proved

⁷ McKeever, F. M. *Tuberculosis of Knee in Infancy and Childhood*, J. A. M. A. **113** 1293 (Sept. 30) 1939.

⁸ Toumey, J. W., Jr. *Surg., Gynec. & Obst.* **68** 1029, 1939.

except by exploration of the joint and verification by laboratory methods. In 146 cases of the series the diagnosis was proved by the observation of tubercles in the sections. The most common presenting complaint was swelling at the knee, the next, pain, and the next, stiffness. Roentgen examination revealed overdevelopment of the epiphyses in frequent instances. After the fusion operation, adult knees were put up in 10 degrees of flexion, as the gait was better with that position, while those of children were placed in 180 degrees of extension. Use of a plaster cast was continued until solid fusion had occurred. There were 14 patients in this series who were 5 years old or less at the time of the fusion operation, the youngest being 2 years of age. Solid bony fusion was obtained in every case in this group, 6 of the patients have been followed from eight to fourteen years.

Tuberculosis of Tendon Sheath—Tuberculosis of the serous bursae about the hand is an uncommon complication of tuberculous infection. Potts⁹ reports 2 cases in detail. Infection in both instances followed trauma. The pathologic process varies with the duration of the disease. At first there is simple synovitis. Later the synovial sheath is congested with reddened elevations, and at this stage tubercles may be found. Adhesions commonly occur. The tendon may become frayed and necrotic. The symptoms are those of a slow progressive swelling followed by stiffness and occasionally tenderness. A sinus may form. The characteristic lesions produced by tubercle bacilli must be found to establish the diagnosis. Treatment consists of care in a sanatorium and rest of the part. Roentgen therapy has been helpful. Surgical extirpation may be considered if removal of the diseased tissue will not interfere with future function of the hand.

OSTEOMYELITIS

Complications of Osteomyelitis—Hobart and Miller¹⁰ have observed 17 cases of carcinomatous degeneration of the skin associated with chronic osteomyelitis in a series of 4,796 cases of the latter condition. They report in detail 7 cases of carcinoma and 2 cases of "toxic deafness of the eighth nerve" complicating osteomyelitis. The age of the patients in the group with cancer varied from 52 to 73 years, the duration of the infection was from one and one-half to fifty years. The lesions were all in the lower extremities, in 6 cases below the knee, and in 1 in the thigh. The symptoms were a chronic discharge, slight local pain, a foul odor and (in 3 cases) hemorrhage. In 5 of the 7 cases amputation was done, in 1 a wide curettement with an Orr petrolatum pack was done, and 1 patient died before the necessary operation could

⁹ Potts, F. N. New York State J. Med. **39**: 983, 1939.

¹⁰ Hobart, M. H., and Miller, O. S. Am. J. Surg. **45**: 53, 1939.

be performed. No recurrence or metastasis has been observed in any of the remaining 6 patients in a follow-up of one to three years. The roentgenograms revealed nothing characteristic of malignant invasion of soft tissues but in some instances showed suspicious moth-eaten areas with rarefaction. The histologic picture in 6 instances was that of squamous cell carcinoma, in the seventh the pathologic tissue was diagnosed as sarcoma.

Present Status of Chronic Osteomyelitis—McCarroll and Key¹¹ describe 200 consecutive cases of chronic osteomyelitis. Forty-one of the patients had been treated for more than one week with an erroneous diagnosis during the acute stage of the process. In only 9 was the bone drained during the first week of the disease. Consequently, about 191 of these patients had been treated conservatively or by delayed operation. In this entire series the incidence of secondary osseous foci was 25 per cent, and that of involvement of the neighboring joint was 50 per cent. By means of standard surgical procedures and prolonged hospitalization with adequate after-treatment it was possible to obtain healing in only 61.3 per cent of 98 patients who were followed for three years or longer. In 38.7 per cent of these the sinuses continued to drain or the disease healed and recurred during the period of observation. Of their series of 200 cases the authors consider their end results poor in 35.5 per cent, fair in 28 per cent, good in 25.5 per cent and unknown in 11 per cent. In conclusion they state the belief that cure of the disease depends on the ability of the surgeon to perform an adequate operation and remove all of the infected bone and that the type of after-treatment is relatively unimportant provided adequate drainage is maintained. Forty per cent of the patients in whose cases adequate surgical treatment was not feasible remained practically incurable. Furthermore, the authors express the opinion that early diagnosis of acute hematogenous osteomyelitis and prompt draining of the focus in the bone are the most important factors in prevention of chronic osteomyelitis and its attendant economic waste and crippling. The actual treatment is as follows. The operation is performed under a tourniquet when one can be used. After wide saucerization is completed, the wound is packed with dry, fine mesh gauze in order to control bleeding, and a dry dressing is applied. A cast is not applied unless there is danger of a fracture of the residual shaft or of the involucrum. On the third postoperative day the gauze pack is removed with the patient under nitrogen monoxide and oxygen anesthesia, and a petrolatum gauze pack is inserted. This is changed at intervals of from two to four days. After the first two or three dressings the wound is lined by granulation tissue, and little pain is experienced by the patient. If at any time the granulations do not appear healthy,

¹¹ McCarroll, H. R., and Key, J. A. Surg., Gynec. & Obst. 68: 1007, 1939.

wet dressings are used and the wound is irrigated with physiologic solution of sodium chloride for a few days. Petrolatum gauze is then substituted. In addition, the Carrel-Dakin method and various types of wet dressings have been used.

[ED NOTE This gloomy picture of the result of treatment of chronic osteomyelitis shows that there is great need for further investigation of this disease. In this review a number of the newer procedures, such as chemotherapy, toxin therapy and roentgentherapy are not mentioned.]

CHRONIC ARTHRITIS

Orthopedic Treatment of Strumpell-Marie Arthritis—Swaim's¹² report is based on the study of 106 cases of advanced spondylitis extending over a period of twenty-two years. There were 22 female and 84 male patients. The deformity in this disease presents itself as a long bend of the whole spine, with a reverse curve in the lumbar region, so that in standing the pelvis is actually tipped backward, and constant strain is thrown on the hip joints. Involvement of the hip appears to be secondary to the strain induced by bad posture and loss of normal lordosis. Rarely, lateral curvature is produced by unequal spasm. The progress is slow, and, except for the hips, rarely attacks the extremities except in women. The treatment adopted by the author is as follows. First, the posture is improved by recumbency. If the spine is not corrected in two weeks, a jacket is applied. The patient is placed on a Goldthwait frame, which is bent to produce lordosis. Then a light plaster jacket, well padded over the spine, the anterior superior spines of the ilium and the sternum, is applied. The jacket is molded tightly over the abdomen to limit abdominal breathing, to force the chest up and to compel expansion of the upper part of the chest. It is left high in front and cut just below the shoulder blades in back, so that with each breath the chest is forced against the jacket in front, thus straightening the thoracic portion of the spine. The jacket extends to the symphysis in front and the tip of the spine in back and grips the pelvis firmly. There must be no space below the jacket in front which will permit abdominal breathing. Most of the patients are more comfortable when held firmly, and they dread having the jacket removed. The jacket is kept on uninterruptedly for several weeks, until all spasm has gone. Then a new jacket is made. Plaster jackets are applied until the best possible correction has been obtained. Then a more permanent leather jacket is made. Although 62 patients have worn jackets, the author chooses only 23 cases from which to draw conclusions, because in these the jackets have been worn for from four to nine years. Of the 23 cases, the good posture thus obtained was maintained in 5, improved in 15 and

¹² Swaim, L. T. J. Bone & Joint Surg. **21** 983, 1939.

lost in 3. One of the patients refused the jacket after two years, 1 cut his jacket in front, so that it no longer supported, and 1 was uncooperative. No trouble with the hip developed in any of the 62 cases. In the group of 23 patients who wore jackets from four to nine years, 11 had symptoms referable to the hip at the beginning, and 7 of these became completely symptomless, the 3 patients with fused hips showed no change, 1 patient became unaccountably worse. Expansion of the chest decreased in 7, was unchanged in 2 and increased in 14 patients. Weight increased in 20, remained the same in 2 and decreased in 1. Sixteen patients are working, 6 are at home, unemployed but looking for work, and 1 died of carcinoma of the breast. In 13 cases some ossification of the ligaments was present before the jackets were used, and in these cases the bridging increased in spite of the jackets. Seven of the 23 patients showed no bridging at first, but later 4 of these had one or two bridges, usually at the twelfth thoracic or the first lumbar vertebra. Three of the 7 showed no bridging, even at the end of four, five and eight years respectively. Although there are too few cases and the period for which the jackets were worn is too short to enable one to draw final conclusions regarding prevention of ossification, this study strongly suggests that ossification is much less rapid in patients treated with jackets. Excellent photographs accompany the text.

SPINE

Persistent Epiphyses of the Vertebral Process—Bailey¹³ has found that secondary centers of ossification may appear opposite the tips of any of the major vertebral processes. The transverse processes regularly have secondary centers. The inferior processes frequently have them, and they occur occasionally in the superior articular processes and in the spinous processes. These secondary centers may persist into adult life and are frequently confused with fracture. Ossification of a vertebra begins at the age of 8 weeks in three centers, one for the body and one for each half of the neural arch. A ringlike center of ossification develops at the periphery of the cartilaginous plates at each extremity of a vertebra at about the seventeenth year and fuses with the body of the vertebra at about the twentieth year. This ringlike center is seen in profile in a lateral view as a small triangular piece of bone. Differentiation of persistent epiphyses in the vertebrae from fracture can usually be made. Ordinarily there are severe pain and disability from fracture, and fracture fragments are usually more displaced. A fracture line is serrated, while an epiphysal line is smooth, and the epiphysis has a definite cortex parallel to a cortex on the opposing surface. A final point is that persistent epiphyses are often multiple or bilateral.

¹³ Bailey, W. Am J Roentgenol 42:85, 1939

Pain Low in the Back Caused by Protrusion of the Intervertebral Disk—Craig and Walsh¹⁴ discuss pain low in the back and sciatic pain resulting from protruded intervertebral disks and hypertrophied ligaments. The cause of this condition is probably traumatic, and the trauma may produce injury to other structures. Thus, it was found that of the 175 patients with herniated intervertebral disk most recently observed, 155 had an associated hypertrophy of the ligamenta flava. Statistical analysis of the cases of 300 patients in whom protrusion of the intervertebral disks was verified at operation reveals the following data: 1. The 300 cases in which a diagnosis of probable protruded disk had been made were selected from approximately 10,000 cases of pain in the lower part of the back and sciatic pain observed in three years. Three hundred and thirty-two protrusions were found in these 300 cases. There were protrusions in the lumbar region in 285 cases and in the cervical and thoracic regions in 15. In 270 cases the protrusions were single, and in 30 cases they were multiple. Thirty were at the third lumbar interspace, 140 at the fourth lumbar interspace and 139 at the fifth lumbar interspace. Of the 300 patients, 226 were men and 74 were women. The average age at operation was 40 years. One hundred and seventy-six (59 per cent) gave a history of injury. In 37 per cent of the cases the patient recalled that injury immediately preceded the symptoms. In 81 per cent there was intermittence of symptoms. Unilateral sciatic pain was the most common symptom, bilateral sciatic pain occurred in 15 per cent of the cases. In 174 cases the value for protein in the spinal fluid was 40 mg. or more per hundred cubic centimeters, in 91 cases it was below 40 mg. There were no deaths in the series. In no case was it necessary to do a fusion operation to relieve postoperative pain.

SHOULDER

Calcification of the Supraspinatus Tendon—Bishop¹⁵ studied calcareous deposits about the shoulder and found that they are more common than is generally believed. One fourth to one third of the patients showed deposits in both shoulders, only one shoulder being symptomatic at the time of examination. Calcification in the supraspinatus tendon usually occurred between the thirtieth and the fiftieth year. The tendon of the supraspinatus muscle reinforces the central portion of the capsule and is inserted into the anterior and uppermost part of the greater tuberosity. The thin synovial lining of the subacromial bursa is tightly adherent to the tuberosities and to the adjacent part of the conjoined tendons. Bishop discusses the etiology and feels

14 Craig, W. McK., and Walsh, M. N. *Minnesota Med.* 8:334, 1939.

15 Bishop, W. A., Jr. *Calcification of Supraspinatus Tendon. Cause, Pathologic Picture and Relation to Scalenus Anticus Syndrome*, *Arch. Surg.* 39:231 (Aug.) 1939.

that repeated minor traumas may cause rupture of a few fibers of the tendon. Repeated tearing and healing lead to areas of hyaline degeneration and finally to deposition of calcium. The calcium is located at the base of the bursa, usually in relation to the supraspinatus tendon but occasionally associated with the subscapularis tendon and, less frequently, the infraspinatus tendon. Occasionally the onset of symptoms is abrupt and viciously painful, but usually a history of an insidious onset with an uncomfortable feeling associated with certain movements of the shoulder can be obtained. Pain was grouped into three types: (1) pain localized at the point of insertion of the deltoid muscle; (2) constant dull and boring or aching pain near the tip of the shoulder at the point of greatest tenderness, and (3) almost intolerable pain in the muscles of the neck, in the scapular region and occasionally down the arm to the finger tips. This is probably due to reflex spasm of the scalenus anticus muscle of the affected side. The diagnosis depends on careful history taking, physical examination and roentgen examination. A case is presented to illustrate the types of pain encountered. Treatment of acute conditions is by immediate lavage. Subacute or chronic conditions are treated by diathermy or lavage. A small percentage of the patients require surgical removal of the deposit.

Lesions of the Supraspinatus Tendon—Horwitz¹⁶ reviews the pathologic observations in 150 shoulders of 75 cadavers with an average age at death of 55 years. Bursal changes were noted in 30 specimens. These alterations consisted of thickened walls, villus formation and partial or complete obliteration of the cavity. In 10 of the shoulders there were communications between the bursa and the joint, due to a tear of the supraspinatus tendon. There were 10 complete tears of the musculotendinous face, of which 3 were bilateral and 4 were unilateral. The youngest subject in these cases was 50 years of age. In 49 shoulders there was a variable amount of thinning of the cuff, and in 30 instances the superficial surface was frayed and fibrillated. Constriction in the biceps tendon in the groove was seen. In 75 shoulders varying stages of flattening, thinning, fraying and fibrillation were evident. In 4 cases complete tears were noted, with reattachment of the distal portion of the tendon to the region of the lesser tubercle. In 1 case the tendon was bound down by adhesions. The bony changes were proportional to the alterations in the soft tissue. Bony recession and atrophy of the greater tubercle were found in the cases in which complete tears of the tendon had occurred. Occasionally the joint cartilage was denuded in areas. The author feels that rupture of the supraspinatus tendon represents the

¹⁶ Horwitz, M. T. Lesions of Supraspinatus Tendon and Associated Structures. Investigation of Comparable Lesions in Hip Joint, Arch Surg 38:990 (June) 1939.

effects of trauma, often minimal, on tissues which are the site of degenerative lesions incidental to advancing age, defective circulation, excessive use and attritional changes. Trauma serves merely to hasten the progress of pathologic events already taking place. The wisdom of subjecting the patients to surgical procedures is therefore to be questioned. This does not apply, however, to patients who have not reached the fourth decade of life.

KNEE

Injuries to the Meniscus—Efskind¹⁷ reports the end results of 36 operations for injury to the semilunar cartilage performed between 1928 and 1936. At operation 32 torn cartilages were found. One patient had cysts in the cartilage, and in 3 instances nothing abnormal was found. All but 2 of the patients have been followed by the author to the present time. In 40 per cent the knee is functionally and anatomically normal. All of these patients have returned to their regular work except 20. Diminution in the joint space where the cartilage was removed was common. Abnormal static changes occurred with defects in the articular cartilage in 13 patients, without any change in the knee not operated on. Occasionally there were changes also in the synovial membrane and fat pad.

Injuries to the Knee in Athletics—Hopkins and Huston¹⁸ studied the end results of 193 severe injuries to the knee. All of the patients were young men attending Springfield College. There were 19 patients with traumatic synovitis. In only 1 case was aspiration performed. Support of the knee with a bandage was the usual treatment. A satisfactory end result was obtained in 17 cases, an average period of four weeks being required for complete recovery. In 2 patients there were recurrent pain and swelling after exercise. In 59 patients a strain of the lateral ligament occurred, in 54 of the internal ligament, and in 5, of the external ligament. Treatment consisted of crutches, tight bandage and physical therapy. The average time lost from athletics was three weeks. While immediate recovery appeared to be good in all but 4 cases, less than half of the patients have remained free from symptoms. The chief complaints are of pain and swelling with vigorous use. The writers suggest that there may have been an associated injury to the semilunar cartilage which could not be demonstrated at the time of injury. There were 139 injuries to the semilunar cartilages. Fifty-three of these were treated by rest, support and physical therapy. Thirteen required removal of the cartilage later. Treatment by rest, support and physical therapy gave good end results in only 19, or 36 per cent. In 24 cases of injury to the semilunar cartilage a plaster cast

¹⁷ Efskind, L. *Acta chir Scandinav* 82:499, 1939.

¹⁸ Hopkins, F. S. and Huston, L. L. *New England J Med* 221:95, 1939.

was worn for an average of four weeks and clutches were used. The end result was good in 18, or 66 per cent. Eleven patients originally treated by immobilization in plaster required operative removal of the cartilage later. There were 22 patients with probable injury to the semilunar cartilage. An exact diagnosis could not be made. All of these were treated with rest and support to the knee. Seven still have slight disability. The authors feel that immobilization should be tried in all cases of injury to the semilunar cartilage before operation is resorted to.

[ED NOTE: In cases of severe injury to the knee an exact diagnosis often cannot be made immediately. In such instances prolonged support is indicated until the extent of the injury can be determined.]

Treatment of Weak Feet—Graham¹⁹ divides weakness of the feet into three types: (1) that due to postural deficiencies, (2) that resulting from a shortened achilles tendon, and (3) that due to anatomic deformities of the bones. He states that in the condition due to postural faults a valgus of the posterior part of the foot occurs from an attempt to adjust to the line of gravity, which in faulty posture with increased forward inclination of the pelvis comes anterior to the acetabulum. To bring the weight thrust anterior to the acetabulum the femoral column rotates internally. Since no rotation is possible at the knee or ankle, this rotation must take place at the subastragalar joint, with resulting valgus. The anterior part of the foot follows the os calcis into eversion and abduction. This rotatory movement is increased as the astragalar head moves medialward. As the os calcis is tilted, the astragalus becomes more depressed, with lowering of the inner side of the foot. With locomotion a relative dorsiflexion of the anterior part of the foot and hypermobility of the first metatarsal segment occur and are followed by splaying of the front portion of the foot. A relative break occurs in the midsection of the foot, and this may be followed by abduction and supination of the anterior portion. A short achilles tendon may be compensated by high heels, with marked diminution of function in the metatarsal joints. With low heels, valgus results in an attempt to bring the heel to the ground. In his discussion of weakness of the feet due to anatomic deformities the author mentions shortness of the first metatarsal bone and the posterior location of the sesamoid bones beneath it. The metatarsal bone extending farthest forward must act as the principal fulcrum. When the second metatarsal is longer than the first, the foot becomes pronated and abducted to permit functional use of the first metatarsal bones. In treatment of weak feet the causes must be eliminated, particularly with the first and second types. In cases of acute involvement with synovitis and

¹⁹ Graham, J. *Illinois M J* 75 425, 1939

myofascitis the author advises rest with the foot fixed in varus. Supports are worn for four to six weeks. They are then gradually discarded, and the threshold of muscular fatigue is raised by exercise.

[ED NOTE This careful analysis of the mechanics of weak feet is commendable. In most cases the use of supports and muscular reeducation must be continued for longer periods than are suggested in this article.]

NEOPLASMS

Angioendothelioma of Bone—A brief review of the knowledge of this type of tumor is given by Lutz and Pusch²⁰. Clinically the growth does not differ from other forms of sarcoma. Growth is rapid, and pulsation may be present. The tumor is generally solitary. Roentgen examination shows a bulky cystlike formation with fine lacelike trabeculae throughout. The wall is defined and has a tendency to blend with the soft tissues. Marked destruction of bone is present without production of bone. The growth often resembles a giant cell tumor. It has been seen in the long bones, ribs, pelvis and vertebral column. It is somewhat radiosensitive. Metastases are commonly found in the lungs. Microscopically the tumor is characterized by blood-filled tubular columns of cells with bulky clear cytoplasm. A case of angioendothelioma of the humerus in a woman aged 54 is presented in detail.

Xanthomatous Tumors of Joints—De Santo and Wilson²¹ present a complete study of this interesting condition, including 9 case histories with photographs, roentgenograms and photomicrographs. Xanthoma of the synovial membrane of the joints is probably more common than has been hitherto supposed, as is exemplified by this group of 9 cases collected in a brief period. The preoperative diagnosis of articular xanthoma seems never to have been made. Obscure intermittent swelling of the knee joint associated with pain and free fluid, occasional locking and a movable tumor, usually medial to the patella, frequently are caused by xanthoma. Aspiration of the joint with recovery of dark or sanguineous fluid points to the presence of tumor. The demonstration of a large amount of cholesterol in the fluid is probably pathognomonic of xanthoma. Xanthoma originates in chronic hemorrhagic villous arthritis. The stroma cell is related to the reticuloendothelial system. It is derived from the surface mesothelium of the synovial membrane, which has reticuloendothelial properties, and gives rise to (a) the foam cell, (b) the giant cell and (c) the pigmented cells associated with xanthomatous disturbance of lipid metabolism. The value for blood cholesterol is frequently elevated. Cholesterol formation

²⁰ Lutz, J. F., and Pusch, L. C. *Angio-Endothelioma of Bone*, J. A. M. A. **113** 1009 (Sept. 9) 1939.

²¹ De Santo, D. A., and Wilson, P. D. *J. Bone & Joint Surg.* **21** 557, 1939.

probably takes place locally as a result of interstitial hemorrhage, and the cholesterol is a product of decomposition of hemoglobin. Its failure to be formed universally when interstitial hemorrhage occurs is partially explained by the systemic disturbance of lipid metabolism which usually exists. Xanthoma of a joint can be cured by radical excision. In the case of a solitary tumor local excision is sufficient, but in the case of multiple or diffuse xanthoma subtotal or total synovectomy is usually necessary. No instance of a benign giant cell xanthoma undergoing malignant transformation was found.

MISCELLANEOUS

Traumatic Fat Embolism—Whitaker,²² discussing traumatic fat embolism, states that the chief source of fat is injured bone and that the fat is drawn or forced by compression into torn haversian canals, which do not collapse as veins do elsewhere when torn across. Pressure exerted by extravasation of blood and serum into tissues tends to force liberated fat into the veins. If a cast is applied before maximum swelling of tissues is reached there is a tremendous increase in this pressure. The fat goes to all parts of the body but the symptoms are usually referable to the lungs and the brain. Two cases are presented, in 1 of which there were pulmonary, in the other profound cerebral, signs and symptoms. Both patients made complete recovery. A petechial rash and detection of fat in the urine are helpful diagnostic signs. Treatment is symptomatic. More can be done to prevent than to treat fat embolism, and one of the most important points is careful handling and manipulation of injured bone.

Gas Gangrene in Civil Life—In an editorial²³ in *The Journal of the American Medical Association* it is stated that the death rate from gas gangrene is still appallingly high. In Millar's series of 607 patients in civil life there was a mortality rate of 49.7 per cent, while the mortality from the same infection in the American Expeditionary Forces in France was 48.52 per cent. Eliason, in 349 cases of gas gangrene following amputation for arteriosclerotic or diabetic gangrene, recorded a mortality of 59 per cent for the entire group and 75 per cent for diabetic patients. In a group of cases in which operations other than amputations were performed the mortality was 41 per cent with serum and 76 per cent without serum. Two facts largely responsible for the lack of awareness of gas gangrene by physicians are (1) that gas

²² Whitaker, J. C. Traumatic Fat Embolism. Report of Two Cases with Recovery, *Arch. Surg.* **39** 182 (Aug.) 1939.

²³ Gas Gangrene in Civil Life, editorial, *J. A. M. A.* **113** 234 (Jul. 15) 1939.

gangrene is rare in time of peace and (2) that it always presents itself in the typical grave form. Gas gangrene is caused almost exclusively by anaerobic bacilli. Deeply lacerated, contused, soiled wounds, compound fractures, hematoma and interference with blood supply create favorable conditions for the growth of anaerobes. The local signs are rapidly increasing swelling, serous or serosanguineous discharge, mottled discoloration of the skin, crepitation of tissues and escape of gas from the wound with the characteristic odor. Early roentgenograms showed gas deep in the tissues. Serum is definitely indicated for both prophylaxis and treatment. Judgment as to sulfanilamide and roentgen therapy must be suspended until further experience is obtained.

Gas Gangrene—Newell²⁴ reviews the diagnosis and the present day treatment of gas gangrene. About twenty-five varieties of anaerobic organism have been isolated, the chief ones being *Clostridium welchii*, *Clostridium oedematis maligni* (vibron septique) and *Clostridium oedematiens*. The diagnosis rests mainly on severe pain, a high pulse rate, edema and brownish discoloration of the skin. There may be a mousy or putrid odor or no odor. Roentgenograms may show gas bubbles in the tissues, and subsequent ones taken at four hour intervals demonstrate an increase in the number of bubbles. Crepitus of the tissues is a relatively late finding. If the infection is due to vibron septique, there will be only edema and no gas formation. In regard to treatment, it is generally concluded that the prophylactic injection of gas antitoxin does not prevent gas infection but that it probably lengthens the incubation period and lessens the severity of the attack. Polyvalent gas antitoxin in doses of 10,000 to 30,000 units should be administered intravenously every six to eight hours. Roentgen therapy is a definite aid in treatment, but it seems desirable to use serum with it. For local use, dilute solution of sodium hypochlorite, hydrogen peroxide or 1:500 potassium permanganate solution is indicated. Sulfanilamide has been used recently, and the results have been encouraging.

Dislocation of the Extensor Tendons in the Hands—Straus²⁵ reports that dislocation of the extensor tendons in the hands is a rare injury. There are immediate disturbance of function and swelling of the dorsum of the hand. The swelling soon subsides, but interference with extension is permanent unless it is repaired. The author reports in detail the history of a case of dislocation of the extensor tendon at the third metacarpophalangeal joint. Operative exploration showed a V-shaped tear in the tendon permitting the intact lateral half of the tendon to slide to the ulnar side. The tear was sutured, and a reten-

24 Newell, E. D. *Ann Surg* **110** 100, 1939.

25 Straus, F. H. *Ann Surg* **111** 135, 1940.

tion ship of fibrous tissue was turned over the tendon from the ulnar side and sutured to the soft tissues on the radial side. Normal function was regained after this procedure.

Kienbock's Disease of the Carpal Navicular Bone—Cave²⁶ states that fewer than 100 cases of this lesion have been recorded in the literature. At the Massachusetts General Hospital the diagnosis has been made 5 times. In regard to etiology, it is generally agreed that severe trauma is not necessary to produce necrosis of the carpal navicular bone, but in the majority of the cases trauma is present. Trauma results in tearing of the dorsal ligament and subsequent interruption of the blood supply followed by aseptic necrosis of the bone. In 1 of the author's cases microscopic examination showed an extensive necrotic process subjacent to the articular cartilage. There was an occasional focus of apparent new bone formation. Several groups of foreign body giant cells were observed. The diagnosis depends on the roentgen findings. In the anteroposterior view one may see early cyst formation and irregularity of the radial surface, with localized areas poor in calcium and other areas with marked increase in the calcium content. As the disease progresses the bone becomes dense, smaller and irregular in outline, taking on the appearance of a sequestrum. In the lateral roentgenograms the density of the bone is increased. The disease commonly occurs in young men who do heavy work. There is a history of slow but definite increase in pain, moderate stiffness and thickening of the wrist joint. Thickening is most marked over the dorsum, in the central portion. Local tenderness is usually acute and is sharply localized to the center of the dorsum of the wrist. In the acute stage, active motion in any direction may be painful. If the diagnosis is made early, conservative measures, consisting of support from a plaster or leather wristlet, may help to restore nutrition to the bone and prevent advance of the process. When the bone is permanently deformed, however, and has the appearance of an irregular sequestrum, or when it has disintegrated, the treatment is excision, with great care to avoid trauma to surrounding structures. Good recovery of function in the wrist joint, with little or no pain, may be expected after the diseased lunate bone has been removed.

FRACTURES

Resection of the Radial Head and Neck—After a study of 13 cases of resection of the radial head and neck King²⁷ reports the end results as follows: in 1 case, excellent, in 5, good, in 4, fair, and in 3, poor. One of the chief factors which cause disability is bone formation at the operative site. The author feels that this may be minimized if the fol-

²⁶ Cave, E. F. J. Bone & Joint Surg. **21** 858, 1939.

²⁷ King, B. B. J. Bone & Joint Surg. **21** 839, 1939.

lowing points are stressed 1 Complete removal of all free or loosely attached bone fragments, periosteal shreds or strips and capsular tissue at the time of resection 2 Avoidance of stripping back the periosteum from the radial stump unless the stripped-up portion of the periosteum is completely excised or sutured over this stump to form a limiting membrane 3 Use of a free graft of fascia lata snugly approximated with purse string sutures over the end of the radial stump to form a limiting membrane, in case the periosteum has not been so used Another factor which causes disability is proximal displacement of the radial shaft, which may be prevented, as was suggested by Key and Conwell, by snugly approximating the soft tissues with several interrupted purse string chromic catgut sutures to fill in securely the dead space created by removal of the radial head and neck The annular ligament should be repaired It is probably of value to immobilize the wrist in maximum ulnar deviation for two or three weeks after resection of the radial head and neck, in order to allow the formation of scar tissue to obliterate further the dead space which was closed in with interrupted purse string sutures After operation a plaster cast should be applied from the bases of the fingers to just below the elbow, which allows free pronation and supination The arm is supported in a sling, the elbow is flexed to a right angle, with relaxation of the biceps After removal of the cast, "daily active and passive ulnar deviation stretching exercises" are in order The author feels that resection of the radial head should be avoided if possible in the growing child and in the adolescent, because a marked degree of calcification and bone formation frequently follows operative or traumatic insults to this region in the growing child Four of the 5 patients in this group who showed no appreciable bone formation following resection were 21 years of age or older

Ununited Fractures of the Carpal Navicular Bone—Edelstein²⁸ reports 6 cases of ununited fracture of the carpal navicular bone seen from three months to nine and one-half months after injury In each case bony union resulted from a bone-drilling operation, which he describes He states the opinion that when sclerosis is present between the fragments in an old fractured navicular bone union will not take place Instead, severe arthritis supervenes and becomes progressive, involving the immediately neighboring intercarpal joints and the radio-carpal joint The navicular bone possesses little periosteum to assist in the formation of subperiosteal callus The formation of bone in the callus is slower than in other fractures, owing to the poor blood supply The bone has only a small surface posteriorly and anteriorly for the attachment of ligaments Elsewhere it is covered with cartilage Its

28 Edelstein, J M J Bone & Joint Surg 21 902, 1939

blood supply is derived from two vessels, one of which penetrates the tuberosity. Therefore, a fracture through the waist of the bone renders the proximal fragment avascular. Because of the poor blood supply, union takes a long time for the vessels have to grow from the peripheral into the central fragment. These fine capillary vessels are ruptured with the slightest shearing movement, hence the necessity for complete immobilization. With adequate and early immobilization nonunion should never occur.

Treatment of Obstetric Fractures of Femur—For obstetric fractures of the femur Pavlik²⁹ advises reduction of the fracture and retention of the limb in abduction by means of a plaster of paris cast symmetrically applied to both lower extremities in a similar manner to the application of a cast for the treatment of congenitally dislocated hips. The treatment has the advantage of simplicity. It does not require hospitalization. During the first month the plaster is changed each week, the final bandage is worn for one month, and treatment is usually terminated at the end of two months, at which time the callus is sufficiently strong. This method has been used for the past three years. In each case the fragments have healed satisfactorily without appreciable shortening of the limb.

Excision of the Fractured Patella—Dodd³⁰ gives an account of 5 consecutive cases of fractured patella treated by excision of the fragments. The operation is carried out as soon after the accident as conditions permit, if possible, on the same day. After the fragments have been removed, the quadriceps tendon is closed by interrupted thread sutures, on the seventh day after operation flexion of the knee is practiced over the side of the bed, and walking with a cane begins on the tenth day. In all 5 cases normal function was obtained.

[ED NOTE Occasional reports have appeared of removal of the patella, which has been regarded as a sesamoid bone. Sufficient time has not elapsed, however, to determine whether removal in any way disturbs the mechanics of the knee joint.]

Pseudofracture of the Tibia—Roberts and Vogt³¹ present 12 cases of what they consider a clinical entity involving the upper third of the tibial shaft in children between the ages of 4 and 16 years. The roentgen appearance may simulate a fracture, but the condition is not due to acute trauma. The cause is not known but may be a chronic infectious process. The pathologic reports on 2 of the patients in whose cases biopsies were done and the fact that slight fever and leukocytosis were present in 3 of the cases suggested this. It is suggested that the so-called

²⁹ Pavlik, A. J. Bone & Joint Surg. **21** 939, 1939.

³⁰ Dodd, H. Lancet **2** 130, 1939.

³¹ Roberts, S. M., and Vogt, E. C. J. Bone & Joint Surg. **21** 891, 1939.

pseudofracture line may be influenced by the course of a nutrient artery. The arguments against classification of the condition as a fracture are as follows: 1 Except in 1 case, there was no history of trauma adequate to cause a fracture of the tibia. 2 Transverse incomplete fracture of the upper end of the tibia must be extremely rare in this age group, as no case could be found in the records of the fracture service of the Massachusetts General Hospital for the years 1920 to 1937, and only 1 case was observed at the Children's Hospital. 3 Roentgenograms taken within a few days of the onset of symptoms did not show any line suggestive of a fracture, but after two to four weeks or more the roentgen appearance began to suggest a fracture line. 4 The amount of subperiosteal new bone formation was greatly in excess of that which would follow even a more severe fracture. 5 Three patients had evidence of recent infection elsewhere in the body. 6 In 1 case the condition was bilateral. 7 In 1 case there was a recurrence of the disease five months after the original attack had been practically cured. All of the patients improved with rest and immobilization in plaster and eventually became free from symptoms. Others were given rest in bed followed by limited weight bearing.

ORTHOPEDIC OPERATIONS

Tendon Transplantations—Carpenter³² has reviewed 458 tendon transplantations performed on children. He found that 85 per cent of these operations gave satisfactory results. Poliomyelitis of over eight years' duration responded better than did poliomyelitis of shorter duration. In these cases better results were obtained with *varus* than with *valgus* deformity of the foot. Also, the transplants from tendons which arise from the larger muscles gave better results than did transplants of those from the smaller ones. It appeared to be of no advantage to wait over two years after the acute onset of poliomyelitis before performing the operation. Stabilization of the foot made the tendon transplantations more satisfactory, in fact, secondary operations for stabilization were necessary in 19 per cent of these cases when tendon transplantations had been done without primary stabilization. The type of insertion of the transplant which consists of creation of a bone tunnel and external suture appeared to be the most satisfactory procedure. An analysis of the causes of failure to obtain perfect results showed that errors in surgical judgment were more frequent than errors in surgical skill. In cases of congenital equinovarus, transplantation of the anterior tibial tendon to the mid-dorsum of the foot was the most successful procedure. Transplantation of tendons in cases of cerebral spastic paralysis and of Charcot-Marie-Tooth peroneal paralysis was not effective.

32 Carpenter, A. R. J. Bone & Joint Surg. 21: 921, 1939.

Acetabuloplasty for Dislocation of the Hip—Nachlas³³ describes a new technic for the shelf operation by acetabuloplasty. Through a Smith-Peterson incision the hip joint is exposed. A linear osteotomy is performed through the superior portion of the articular margin. The osteotomy extends into the hip joint. The proximal and distal ends of the osteotomized articular margin are left attached, and the margin of bone is levered laterally. The gap at the site of osteotomy is filled with bone taken from the iliac crest. The hip is put in abduction in a plaster spica for two months, and this treatment is followed by traction on the involved extremity for one month. The prime requisite for the procedure is that the head of the femur be opposite the acetabulum. This may require a preliminary period of traction or an operation to overcome contracture. The procedure was used in 8 cases. These were cases of Legg-Perthe disease with a wandering acetabulum, paralytic dislocations and congenital dislocations of the hip.

New Approach to the Knee Joint—Mader³⁴ states that the patella is the chief obstacle in approaching the knee joint and that it has no important function, being a deterrent rather than an aid to movement. After studies on 20 cadavers had shown that extension of the knee was not disturbed by removal of the patella, he devised an operative approach as follows: a curved infrapatellar incision was made, and the skin flap was reflected upward. The tendon overlying the patella was split longitudinally, and the patella was dissected out subperiosteally. The joint was then exposed by lengthening the longitudinal incision in the quadriceps tendon. This method gave excellent exposure of the joint. Normal function has been observed in the extensor apparatus after the operation.

Amputation for Arteriosclerotic Gangrene—Taylor³⁵ presents a series of 137 major amputations on 117 patients for arteriosclerotic gangrene with or without diabetes. He discusses the relation of the amputation stump to morbidity and mortality. There were 44 deaths, giving an amputation mortality of 32 per cent and a case mortality of 37.6 per cent. In cases of diabetes and arteriosclerotic gangrene the mortality was 34.4 and 52.5 per cent when local or systemic infection was an added complication. In cases in which diabetes was not present the mortality was 27.7 per cent. When "fascial layer closure" was carried out there was a mortality of 43.4 per cent, and nearly half of the deaths (46 per cent) were directly or indirectly due to an infected or a nonhealing stump. The mortality dropped to 19 per cent when

33 Nachlas, I. W. *South M. J.* **32**: 565, 1939.

34 Mader, V. O. *Canad. M. A. J.* **42**: 17, 1940.

35 Taylor, F. W. *Arteriosclerotic Gangrene: Relation of Amputation Stump to Morbidity and Mortality*, *J. A. M. A.* **113**: 1196 (Sept. 23) 1939.

there was no closure and to 16 per cent when a loose skin closure alone was done. Taylor concludes that "anatomic fascial plane suture" of the stump should be reserved for the exceptional case in which there is no infection and an abundant blood supply is present.

Amputation for Advanced Peripheral Arterial Obliterative Disease—This report by Faxon³⁶ is based on 204 single and 58 bilateral amputations. The conditions were subdivided into three clinical entities, Buerger's disease, peripheral arteriosclerosis and peripheral arteriosclerosis with diabetes. Guillotine or amputation preliminary open operation was carried out in 52 instances on critically ill patients as a life-saving measure. The midportion of the lower part of the leg was the site of choice. Secondary closed amputations at a higher level were carried out in 84 per cent of patients who survived the guillotine procedure. Ten per cent of the entire series of patients underwent the open preliminary procedure. Forty per cent of all the patients underwent closed amputations as a primary procedure. In only 5 instances were drains used. It is felt that avoidance of drains in amputation has been a great factor in reducing the mortality from progressive obliterative disease to 13.1 per cent. "Low thigh amputation" is considered the safest of major amputations. The Gritti-Stokes amputation is the most satisfactory for patients whose general condition precludes use of a prosthesis.

Transplantation of the Fibula to the Tibia—Marconi³⁷ after reviewing the various methods which have been used for partial or complete transplantation of the fibula to the tibia reports 4 personally observed cases in which this operation was performed. His first patient was a boy aged 7 years with complete destruction of a portion of the tibia by osteomyelitis. A lateral transplantation was performed of the remaining (upper) end of the tibia to the fibula. Four years later walking was entirely normal. Two operations were necessary to secure union. The second patient was a boy aged 5 years. In his case also there was complete loss of the middle third of the tibia following removal of sequestrums. Transplantation of the fibula into the remaining ends of the tibia was done. Bony union followed the operation. The result eighteen months later showed 3 cm shortening, with some limitation of motion at the ankle joint. There was no other deformity, and the child walked well. The third patient, 4 years old, had a loss of the lower part of the tibia following necrosis from diathermy. A portion of the fibula was implanted into the astragalus below and into

³⁶ Faxon, H. H. Major Amputations for Advanced Peripheral Arterial Obliterative Disease, J. A. M. A. **113** 1199 (Sept 23) 1939.

³⁷ Marconi, S. Chir. d. org. di movimento **24** 552, 1939.

the tibia above. A second operation was required for fracture, with metallic fixation. Two years after the first treatment the patient was beginning to walk and there was solid union. The fourth patient, 16 years old, had lost almost the entire upper third of the tibia from osteomyelitis. An end to end transplant of the fibula was done. There was suppuration for a prolonged period. One year from the beginning of treatment the patient was beginning to walk. The author feels that various modifications of this method must be adopted to secure the best statics in the individual case.

Operation for Correction of Hammer Toe—With the region under local block anesthesia, a hockey-stick cutaneous incision is made on the dorsum of the toe, somewhat lateral to the midline, without a tourniquet³⁸. The flattened tendinous expansion of the extensors, which is intimately interwoven with the joint capsule, is exposed. A tongue-shaped flap with the base attached to the middle phalanx is exposed. A small dorsal bony prominence over the dorsum of the head of the proximal phalanx is sometimes shaved off. A subcutaneous plantar tenotomy and capsulotomy from one collateral ligament to the other are performed. It is important to obtain slight overcorrection of the plantar flexion contracture. The tongue-shaped flap is then resutured with reduplication to the proximal stump of the tendon and capsule by means of fine chromic mattress sutures. If dorsiflexion contracture is present at the metatarsophalangeal joint, it is released subcutaneously with a tenotomy knife in the thorough manner described. The toe is splinted with well fitted, loosely strapped whalebones. Immobilization should be thoroughly carried out for about three or four weeks after the operation. The patient may be permitted to walk a few days after the operation, wearing shoes cut over the toes. In cases in which plantar flexion contracture at the distal interphalangeal joint is also present, fusion is usually performed by shaving off the articular cartilage and performing the capsuloplasty described. In cases in which a painful corn is present at the tip of the toe, a U-shaped incision is made parallel to the distal edge of the nail and slightly to the plantar side. The distal part of the nail phalanx is removed. Seventeen cases (30 toes) are included in this report. Good results were obtained in 14 (26 toes), a fair result in 1 (1 toe) and poor results in 2 (3 toes). The author feels that by this technic the correction of the deformity is obtained with the least sacrifice of appearance and of function.

[ED NOTE While this operation may lead to the most nearly perfect cosmetic result, there are a number of simple but adequate procedures to relieve pain and permit function.]

³⁸ Lapidus, P. W. *J Bone & Joint Surg* 21:977 1939

RESEARCH

Temperature-Controlled Healing of Experimental Fractures—Speed and Fell³⁹ experimented with 66 guinea pigs, 45 of which lived to complete the experiments, to determine the effect of a raised temperature on the healing of fractures. "Both bones of the right foreleg of each animal in one group were fractured in the middle third. All the skin from the mid-upper right leg, down to and including the skin of the foreleg, of each animal in a second group was removed, and an amputation was performed at the wrist joint. The two bones of the foreleg were fractured in a manner similar to that of the first group, and the skinned fractured leg was then inserted into the abdominal cavity through a small aseptic incision made a little below the costal margin. The peritoneum and muscles of the abdominal wall and those of the midportion of the upper leg were sutured together." At the end of four weeks the animals were killed. Seventeen had survived. Of a control group of 10 guinea pigs, in which the bones of one foreleg were fractured and the leg was not buried within the abdomen, 5 tolerated splints from ten to twenty-one days and 5 were not splinted. The fracture area showed bony, fibrous and cartilaginous callus with a histologic picture similar to that observed in the control group. Although the differences in the two groups were not marked, it was felt that the legs which were buried in the abdomen and maintained at a higher temperature than those left outside exhibited a less bulky callus, a more matured bony callus and a much less fibrous and cartilaginous callus than did the unburied legs.

General Reactions of the Skeleton After Fracture—Roche⁴⁰ attempts to show that there are general as well as local reactions which occur in the skeleton after fracture of a single bone. Phosphatase is an enzyme which hydrolyzes phosphoric esters into phosphate ions and produces a concentration of ions favorable to the local production of tricalcium phosphate. Phosphatase is abundant in the skeletal parts of young animals, which are undergoing rapid ossification. The bones of adult animals are nearly barren of phosphatase activity but can be reactivated by certain substances, such as the ionizable salts of magnesium. It has been shown that the callus and the neighboring region of a fracture are the site of increased phosphatase activity, and the author has sought to determine whether this is a purely local affair or whether the entire skeleton takes part in it. Fractures of the humerus in the pigeon were studied and pseudarthroses of the femur in rats were investigated. The following conclusions were reached: 1. The

39 Speed, K., and Fell, E. H. *J. Bone & Joint Surg.* **21**: 1005, 1939.

40 Roche, J. *J. de chir.* **53**: 737, 1939.

callus of fractured bones presents, in general, phosphatase activity of the same order as that of the diaphysial and epiphysial regions of which it is a part. The important augmentation of the phosphatase activity comes a few days after the fracture, before any callus forms, and it disappears in fifteen or sixteen days. These phenomena indicate the putting into play of mechanisms unloosed by the fracture but independent of the evolution of the fracture. Whether the callus is ossified or whether it is converted into a pseudarthrosis, no difference is noted in the modification of enzyme activity in the bone fragments. 2 It was found that the intact bones of an animal with a fractured bone present an increase in phosphatase activity simultaneous with that observed in traumatized bone. The fact that this general reaction occurs early, before there is any possibility of repair, indicates the putting into effect of general mechanisms affecting the biochemistry of the skeleton, which are stimulated or unloosed by the lesion. The author has also made observations on general modifications of the composition of the skeleton after fracture of one bone. Numerous experiments by other authors have demonstrated a slow and progressive resorption of the bony tissue of fractured limbs, which is for the purpose of enrichment of the callus with salts by "local calcium mutation." The author has made the following observations as to general reactions accompanying this local reaction. 1 Modifications of composition appear simultaneously in all parts of the skeleton, being most marked in the immediate site of the lesion. They are characterized at first by demineralization of all the parts during a period of about twenty-five days, followed by a more or less complete repair of the losses previously undergone. This process is independent of the evolution of the callus, occurring even in pseudarthrosis. 2 The intact skeletal bone presents qualitatively the same modifications as the fractured bone at different times in the experiment, though these modifications are less intense in the normal than in the fractured bone. The author concludes from these facts that the skeleton constitutes a physiologically homogeneous system the calcification of which is governed by general, not local, mechanisms.

Effect of Roentgen Rays on Bones—Bade and Kuntscher⁴¹ studied the effect of roentgen rays on the bones of dogs after resection of a piece of the shaft. Marked changes were seen in the bone cells and in the bone marrow after six doses of 400 r each. After such treatment there was no compensatory thickening of the ulna, but fracture from weakening of the ulna was observed in four to six weeks. Histologic studies are not reported.

⁴¹ Bade, H., and Kuntscher, G. Fortschr a d Geb d Rontgenstrahlen 60 235, 1940

Effect of Experimentally Produced Tumors on the Skeletal System—A study⁴² was made to determine the effects of anthracene-produced tumors on skeletal tissue. The agent used was dibenzanthracene. Thirty-five rats were treated, and 16 had tumors ranging in size from that of a pea to that of an orange. Most of the tumors, even though they abutted on skeletal tissue, provoked little or no periostitis, and none showed bone formation. Histologically most of the tumors were cellular fibrosarcomas with elements of rhabdomyosarcoma and liposarcoma. There was no evidence of osteogenic tumor. Periosteal reaction was minimal even when the tumor lay against the outer lamellas of the cortex. In some cases, however, the tumor did invade the contiguous bone and joint to some extent. Intra-articular injection resulted in a sarcoma which invaded most of the structures of the knee joint and extended into the marrow cavity at the distal end of the femur. Implantation of dibenzanthracene into the marrow of the tibia did not produce an osteogenic tumor.

Motion in the Vertebral Column—Elward⁴³ presents an extensive review of the literature on motions of the spine, followed by roentgen studies of the movements of the dorsolumbar and lumbosacral portions of the spine in a 16 year old girl. He concludes from his studies that the range of extension is greater than the range of flexion in the lumbar portion of the spine and that flexion at the hips accounts for the apparent greater range of flexion over extension. In this observation he confirms the work of Brailsford, who found extension to be greater than flexion in the lumbar part of the spine. The work of Wiles and others concerning the slight anterior and posterior displacement of vertebrae on adjacent vertebrae during flexion and extension was not confirmed in this study. The author concludes that the spinal column is not a single hinge but a multiplicity of interacting hinges, or, more precisely, limited universal joints, the nucleus pulposus acting somewhat in the manner of a ball bearing. There is no single center of motion except that of the mass motion centering in the hip joints.

42 Sutro, C. J., and Pomerantz, L. Effect of Experimentally Found Tumors on Musculoskeletal System of Rats, *Arch Surg* **38** 1132 (June) 1939.

43 Elward, J. F. *Am J Roentgenol* **42** 81, 1939.

GENERAL PRINCIPLES OF PREOPERATIVE AND POSTOPERATIVE TREATMENT

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Until relatively recently, interest in advances in surgical technique was definitely greater than that in the preoperative and postoperative treatment of patients. This condition has changed, and it is realized now that the operation is only a part, in some instances a relatively minor one, of the treatment of the patient. Lord Moynihan stated that "surgery has been made safe for the patient and now the patient must be made safe for surgery." The work of the past twenty years has accomplished much in this direction, but probably even greater advances will be forthcoming in the future. Particularly encouraging is the fact that the surgeon is no longer content simply to carry out technical procedures but is interested in the treatment of the patient from a broader viewpoint. The requirement of Sir William Osler, that a surgeon should be a physician who operates, is being more nearly approached. This is due in part to a change in the attitude of the surgeon but to a greater extent to advances in surgical therapeutics.

It is not the purpose of this introduction to the symposium on preoperative and postoperative treatment to consider any of the problems in detail. However, a few of the more important points will be mentioned briefly.

EMERGENCY OPERATIONS

The number of conditions in which immediate operation is considered necessary has declined greatly in recent years. Whereas formerly many patients were taken directly to the operating room on entrance to the hospital, this is a rare occurrence at present. It is realized that in all but a relatively few conditions it is not only permissible but advisable to carry out the proper preoperative preparation, including the pre-anesthetic medication. Massive, uncontrollable bleeding constitutes one of the few indications for immediate operation. Even under these circumstances it is at times advisable to give a transfusion of blood before the operation is performed. In instances of this type the "blood bank" presents a real advantage in that a transfusion can be performed on very short notice. If plasma or serum is used there is no need for any delay.

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HANDICAPPED PATIENTS

There are many patients who present handicaps other than that imposed by the disease which causes the patient to consult the surgeon. Among these handicaps are heart disease, renal disease, hypertension, diabetes and endocrine disturbances, such as hyperthyroidism. Particularly careful preoperative study and therapy are indicated for these patients. Special problems are presented also by infants, by the aged and by the very obese. The advice of a competent internist or pediatrician in the care of these patients is invaluable.

ANESTHESIA

It is only in recent years that intensive studies on the various anesthetic agents have been performed. These have resulted in the carrying out of preoperative measures which protect against the ill effects of some of the agents, in the more intelligent use of preanesthetic drugs, in the better choice of the anesthetic agent and particularly in improvements in methods of administration. It is perfectly obvious that the anesthetic agent should not present a great explosion hazard and that the anesthesia should be adequate to allow the proper performance of the operative procedure. The toxic effects of the agent itself and the ill effects that accompany the causation of anoxia may be less obvious. Much important work has been performed by a number of observers, including Ravdin and his associates, on methods for protecting the liver against the fat-solvent agents. Whether for this purpose or for the prevention of general anoxia with its deleterious effects, the use of a high percentage of oxygen with the inhalation anesthetic agents is extremely important.

BODY FLUIDS AND ELECTROLYTES

It is only in recent years that the full significance of the dehydration that may result from insensible loss of water, from vomiting and diarrhea and from other causes has been fully appreciated. The findings of Gamble and his associates and of Collier and Maddock are of particular interest from the surgical viewpoint. A number of methods have been described for determining the fluid and electrolyte requirements. It is important that fluids be given in such quantity and quality that the output of urine is at least 1 liter per day.

It should be emphasized that in many patients with surgical conditions there are large losses of water and electrolytes. Replacement of both is a necessity, since water alone cannot be retained. Qualitatively in the giving of electrolytes, one naturally should attempt to replace what has been lost. Hence, if the loss is mainly chloride, salt solution should be given, and if the loss is mainly bicarbonate, one should give either bicarbonate or some fluid which on oxidation yields bicarbonate. Quantitatively one should bear in mind the relation between the loss and the replacement therapy. As has been stated a number of

methods are available for determining the loss. For more retention of the fluids administered does not guarantee a proper partition of these fluids in the body. This is particularly true if there is a deficiency of blood colloids. Under this condition, more of the injected fluid will be retained in the circulatory system if the abnormality in plasma composition and volume is corrected by the introduction of blood serum or plasma.

When disturbances in the acid-base balance occur in the presence of adequate renal function, correction can usually be accomplished by administration of adequate quantities of saline and dextrose solutions. The incorporation of minute amounts of cations in other various repair solutions which have been suggested seems to offer no particular advantages over simple saline and dextrose solutions. The problem is more complicated in the presence of marked renal impairment.

MALNUTRITION

One of the undesirable features of malnutrition is the hypoproteinemia which often accompanies it. Protein is of great importance in maintaining the osmotic pressure in the blood vessels, thereby counterbalancing the filtration pressure. In the presence of a low protein content of the blood plasma, edema of the tissues frequently occurs. It has been shown that this is apt to result in retardation of the healing of incisions, nonfunctioning of intestinal anastomoses and an increase in pulmonary complications. Methods for correcting the protein deficiency include the giving of a balanced diet by mouth when this is feasible and the use of transfusions of whole blood or plasma.

It is only in recent years that particular attention has been directed to the ill effects that may result from vitamin deficiencies in patients with disease requiring operation. Particularly important among these from the surgical viewpoint are deficiencies in vitamins C and K. One of the most important functions of vitamin C is the role that it plays in the healing of incisions or wounds. The greatest advance made thus far in the control of the hemorrhagic tendency associated with jaundice has resulted from the discovery of vitamin K. Measures are available for the effective treatment of most of the recognized disorders due to vitamin deficiencies.

PERIPHERAL CIRCULATORY FAILURE OR SHOCK

Advances in the treatment of fully developed shock have not kept pace with advances in the prevention of the condition. After marked damage to the capillaries has resulted from the low blood volume, depressed blood pressure and anoxia, usually no known therapy is of value. The more intelligent preparation of patients for operation and advances in anesthesia and surgical technique are responsible for much of the reduction in the incidence of shock. Particularly important is

the growing appreciation of the value of not allowing the blood volume and the blood pressure to remain depressed. For this purpose the employment of transfusions of whole blood, plasma or serum is most effective. The administration of large quantities of noncolloidal solutions, such as saline or dextrose solutions, does very little good when the capillaries are abnormally permeable, and it may actually result in harm. Fortunately both for the patient and the surgeon, the employment of transfusions of blood or plasma is no longer considered a procedure of last resort. Its greatest field of usefulness lies in the prevention of shock. The results thus far of the use of preserved blood and plasma are most encouraging, and further advances along this line are awaited with interest.

PREVENTION OF COMPLICATIONS

Pulmonary Complications—These continue to constitute one of the most important problems of surgery. In addition to the increase in mortality rate which accompanies these complications, there is an increase in the incidence of the disruption of incisions, and in all instances the patient is rendered uncomfortable as a result of the cough or other symptoms. Whereas there is no known specific treatment that will prevent these complications, a number of measures are helpful. Particularly important are the measures which prevent stasis of secretions in the bronchial tree. These include (1) postural drainage before operation if indicated, (2) avoidance of unnecessarily large doses of sedatives, (3) Trendelenburg position during the operation and until consciousness is regained, (4) removal of secretions with a catheter or bronchoscope if necessary, (5) hyperventilation induced by carbon dioxide inhalations or a rebreathing bag and (6) frequent change of the position of the patient. Sulfapyridine is usually effective in the treatment of postoperative pneumonia.

Thrombosis and Embolism—These are responsible for a good many of the deaths and disabilities which follow operations. The treatment of embolism consists in the main in the prevention of thrombosis. Among the measures which are believed to be helpful in the prevention of thrombosis are (1) gentleness in the handling of tissues during the operation, particularly the large veins, (2) prevention of dehydration and shock, (3) frequent shifting of position of the patient, (4) movement of the extremities and (5) use of anticoagulants, such as heparin.

Intestinal Distention—Distention of the bowel in most instances results more in discomfort than in actual danger to the patient's life. The distention is due in the main to swallowed air and intestinal secretions. Measures which may be effective in therapy include (1) frequent alteration of the position of the patient in bed, (2) use of morphine or pitressin or both combined with use of a rectal tube, (3) inhalation of pure oxygen as suggested by Fine, (4) duodenal suction as accomplished

by the Wangensteen method and (5) use of the Miller-Abbott intestinal tube

The most frequent postoperative complication referable to the urinary tract is retention of urine in the bladder. Aside from the discomfort which the patient experiences, the importance of this complication lies in the fact that stasis is apt to lead to infection. For this reason retention of urine should not be allowed to persist. There are a number of simple measures which may aid the patient in emptying the bladder. If these fail, retention should be treated by the repeated use of a catheter and distention should be avoided.

Only a few of the many points of importance in preoperative and postoperative treatment have been mentioned. The reader is referred to books by Bartlett,¹ Cutting² and Mason³ and articles by Kanavel and Koch,⁴ Cutler and Scott,⁵ Flint,⁶ Ochsner,⁷ Wangensteen and Paine Boland,⁸ Maddock and Collier,¹⁰ Abbott and Johnston,¹¹ Ravdin,¹² McClure and his co-workers,¹³ Holman,¹⁴ Haight¹⁵ and Fine and his associates,¹⁶ to mention only a few, for a detailed consideration of these and other points of importance.

In the papers which follow, preoperative and postoperative treatment will be considered from the viewpoint of the various systems of the body. The subject matter is so great that many phases of the problem are commented on only briefly, if at all. Many authorities responsible for some of the important advances in this field are of necessity, not listed among the contributors.

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PREANESTHETIC MEDICATION

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In a consideration of the chemical agents to be used in preparing a patient for an operation, three factors are of importance

- 1 Which anesthetic agent (basis) is to be used?
- 2 Which of the nonvolatile agents (adjuvants) should be used to produce the preanesthetic depression of the central nervous system?
- 3 Which agents (correctives) should be used to prevent or counteract certain undesirable side reactions produced in the patient by the main anesthetic agent to be employed?

It is a discussion of the agents used as adjuvants and correctives and the reaction of the body to their administration that is to follow

ADJUVANTS FOR DEPRESSION OF THE CENTRAL NERVOUS SYSTEM

The almost universal custom of producing moderate depression of the central nervous system in patients before administration of the major anesthetic agent is based in part on the following points

- 1 The production of a quiet mental state before the patient enters the operating room
- 2 The relief of pain in patients with painful lesions
- 3 The desire to make induction of general anesthesia less difficult for the patient as well as for the anesthetist
- 4 The desire to reduce the concentration of the general anesthetic necessary for a given level of anesthesia, because it is to be expected that this will reduce the frequency of postoperative disturbances attributable to the effects of the anesthetic agents on the tissues of the patient

Opium and Its Derivatives—Morphine and its derivatives diacetyl morphine (heroin, not available legally in the United States) and dihydromorphinone hydrochloride (dilaudid hydrochloride) and the parent group, opium and pantopon or omnopon (mixtures of the pure alkaloids of opium containing about 50 per cent morphine) have been used more widely and over a longer period than all other agents combined. Since morphine is the most important member of this group, the

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discussion will revolve around the reaction of the patient to this drug, with comments relative to the other agents when specific differences are marked

The quantity of morphine necessary to produce the same degree of depression in different patients is dependent on several factors, i. e., size, age, physical state, psychic condition, metabolic rate, etc

The degree or depth of depression that one expects to produce by the preanesthetic agents will vary according to the potency of the anesthetic to be used. When such a drug as ether, chloroform or cyclopropane which is potent enough to produce full anesthesia when used alone is to be employed, the amount of preanesthetic sedatives may be reduced to a minimum, when, however, such an agent as nitrogen monoxide or ethylene, which is not potent enough to produce full anesthesia in the absence of anoxia, is to be used, it is necessary to increase the quantity of the preanesthetic agent so that the concentration or tension of nitrogen monoxide or ethylene in the anesthetic mixture necessary to complete the anesthesia will not be so great as to limit the concentration of oxygen in the required mixture to a value which is inadequate for maintenance of satisfactory oxygenation of the blood and tissues

Kleindorfer and Halsey,¹ Stormont and his co-workers,² Seevers and his associates³ and Robbins and his associates⁴ have shown that the combination of preanesthetic agents (barbiturates, avertin with amylene hydrate, morphine) with nitrogen monoxide or cyclopropane reduces definitely the concentration of these agents necessary for a given level of anesthesia, so that a higher concentration of oxygen may be used when preanesthetic agents are given

In general, doses of 8 to 16 mg of morphine sulfate are adequate and should be given subcutaneously thirty to ninety minutes or intravenously thirty minutes before induction of general anesthesia. If an amount greater than 16 mg is to be administered it should be given in divided doses at ninety and thirty minutes before induction. Seevers

1 Kleindorfer, G. B., and Halsey, J. T. A Study of the Relative Efficiency as "Basal Anesthetics" of Avertin, Amytal, Chloral Dial, and Iso Propyl-Allyl Barbituric Acid, *J. Pharmacol. & Exper. Therap.* **43** 449-456, 1931

2 Stormont, M. F., Lampe, I., and Barlow, O. W. A Comparison of the Premedication Values of Several Barbituric Acid Derivatives in Relation to Nitrous Oxide Anesthesia, *J. Pharmacol. & Exper. Therap.* **39** 165-175, 1930

3 Seevers, M. H., Meek, W. J., Roenstine, E. A., and Stiles, J. A. A Study of Cyclopropane Anesthesia with Especial Reference to Gas Concentrations, Respiratory and Electrocardiographic Changes, *J. Pharmacol. & Exper. Therap.* **51** 1-17, 1934

4 Robbins, B. H., Baxter, J. H., Jr., and Fitzhugh, O. G. Studies of Cyclopropane. V. The Effect of Morphine, Barbitol and Amytal upon the Concentration of Cyclopropane in the Blood Required for Anesthesia and Respiratory Arrest. *J. Pharmacol. & Exper. Therap.* **65** 136-142, 1939

and Pfeiffer,⁵ in a careful study of the analgesic properties of morphine and its derivatives, found that the peak of analgesic effect of morphine is reached in sixty minutes after subcutaneous administration and that the effect at thirty and ninety minutes is near the maximum. When a morphine salt is given intravenously the maximum analgesic effect is observed at thirty minutes. Heroin, which has been used because of its action in depressing the cough reflex, produces its maximum effects at twenty and thirty minutes after intravenous and subcutaneous injection respectively, whereas with dilaudid hydrochloride the maximum analgesic effect is reached at ninety minutes after subcutaneous injection. These observations indicate that if the maximum effect of these agents is desired at the time of induction they must be administered at different intervals before administration of the anesthetic is started. The analgesic effect of dilaudid hydrochloride or heroin is about eight and four times respectively that of morphine.

Barbiturates—Since the introduction of barbital (diethylmalonylurea, or diethylbarbituric acid) by Fischer and von Mering in 1903, over one thousand derivatives of barbituric acid have been prepared in chemically pure form and have been investigated in relation to their action in depressing the central nervous system. At present, barbituric acid derivatives are available some of which on intravenous injection produce immediate anesthesia which lasts for five to ten minutes (evipal, or 5,5'-cyclohexenylmethyl-N-methyl barbituric acid) and some of which produce their full anesthetic effects thirty to forty minutes after intravenous injection, the anesthesia lasting for eighteen to thirty-six hours (barbital). One may select compounds from the remaining nine hundred and ninety-eight odd barbiturates which will produce effects of almost any value between these two extremes in relation to the onset of anesthesia and duration of action. In "New and Nonofficial Remedies" for 1939 a dozen barbituric acid derivatives are listed which may be used as preanesthetic agents, and there are at least as many more in general use in the United States which have not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

The choice, then, of a barbiturate to be used as a preanesthetic agent in place of or in addition to morphine depends on certain factors, i. e., the duration of action expected, the rapidity of onset of action, the route of administration and the therapeutic ratio or index of the individual agent.

⁵ Seevers, M. H., and Pfeiffer, C. C. A Study of the Analgesia, Subjective Depression, and Euphoria Produced by Morphine, Heroin, Dilaudid, and Codeine in the Normal Human Subject, *J. Pharmacol. & Exper. Therap.* **56** 166-187, 1936.

Evipal and pentothal (5,5' ethyl, 1-methylbutylthiobarbituric acid), which are rapidly changed in the body to less active or inert substances cannot be used for preanesthetic medication if it is expected that the effects are to persist for an hour or two, they may, however, be used by intravenous administration for induction of general anesthesia which is to be maintained by an inhalation agent. From the experimental studies of Butler and Bush⁶ it is evident that certain of the 'shorter-acting' barbiturates are changed in vivo to less active substances of longer duration of action. The rate of absorption in relation to the rate of partial inactivation of these compounds which rapidly produce anesthesia of short duration on intravenous injection is such that in order to produce a moderate sedative effect by mouth a dose approximating that which produces full anesthesia when given intravenously has to be administered, for this reason the barbituric acid compounds of short duration of effect are not advised for preanesthetic sedation.

Most of the other barbiturates are either destroyed or excreted at such slow rates that they can be used by oral administration, and if they are given about two hours before induction of anesthesia the full depressant effects will be present at the time of induction.

Barbital, phenobarbital and ipral, which have relatively low therapeutic indexes and very long duration of action, are not advised as preanesthetic agents. The other barbiturates in general use (alurate, amytal, cyclopal, dial, neonal, nostal, pentobarbital, phanodorn, sandoptal and seconal) have relatively high therapeutic indexes as compared with barbital, phenobarbital and ipral, and in most instances the duration of action is intermediate between the very short and the very long.

Barbiturates do not produce appreciable analgesia in the patient and are thus inferior to morphine on this point, but they have certain desired effects on various portions of the autonomic nervous system which morphine does not have. These actions will be discussed later. One may consult Lundy and Osterberg⁷ and Tatum⁸ for reviews of the barbiturate problem.

Avertin with Amylene Hydrate—Avertin with amylene hydrate, which consists of 2 parts by weight of tribromomethyl alcohol and 1 part of amylene hydrate, was introduced as a basal anesthetic and should not

⁶ Butler, T. C., and Bush, M. T. The Metabolic Fate of N-Methyl Barbituric Acids, *J. Pharmacol. & Exper. Therap.* **65**: 205-213, 1939. Bush, M. T., and Butler, T. C. The Metabolic Fate of N-Substituted Derivatives of Barbital, *ibid.* **68**: 278-283, 1940.

⁷ Lundy, J. S., and Osterberg, A. E. Review of the Literature of the Derivatives of Barbituric Acid, *Proc. Staff Meet. Mayo Clin.* **4**: 386-416, 1929.

⁸ Tatum, A. L. The Present Status of the Barbiturate Problem, *Physiol. Rev.* **19**: 472-502, 1939. The Pharmacology of Barbiturates, *Ann. Rev. Physiol.* **2**: 359-370, 1940.

be considered as a preanesthetic agent in the usual sense because of the large amount usually used (0.06 to 0.09 cc per kilogram of body weight or 60 to 90 mg of tribromethyl alcohol and 30 to 45 mg of amylene hydrate). The larger dose at least approaches the full anesthetic dose.

Then, too, amylene hydrate, which is the solvent for the tribromethyl alcohol, has long been used to produce depression of the central nervous system. The dose of this drug alone when used for sedation and administered by mouth is less than that given in the avertin with amylene hydrate. Lehman and Knoefel⁹ and Molitor and Robinson¹⁰ have shown that the addition of amylene hydrate to tribromethyl alcohol, as in avertin with amylene hydrate, has a definite action in depressing the respiratory center as well as in prolonging the anesthesia and sleep following administration of tribromethyl alcohol. Lehman and Knoefel⁹ and Molitor and Robinson¹⁰ have also shown trichlorethyl alcohol to be more stable and more soluble, as well as to have a greater margin of safety than tribromethyl alcohol (avertin). It may be that trichlorethyl alcohol will replace avertin with amylene hydrate as a basal anesthetic.

CORRECTIVES IN GENERAL ANESTHESIA

Hyoscine, Scopolamine and Barbiturates—Atropine and scopolamine are employed as preanesthetic agents primarily because of their inhibitory action on portions of the cramosacral (parasympathetic) division of the autonomic system. Leake¹¹ stated "Atropine was introduced as an adjunct to chloroform anesthesia in order to prevent the reflex stoppage of the heart during induction of chloroform anesthesia by paralyzing the peripheral endings of the vagi." In relation to the use of scopolamine (hyoscine) he stated "In the absence of any critical evaluation of its usefulness as a preanesthetic hypnotic, there seems little justification for its continued employment merely because of clinical routine or habit. It is chemically related to atropine and has somewhat the same type of action as atropine on the autonomic nervous system. This has no special value in preanesthetic medication, but may introduce deleterious factors." Others particularly Guedel¹² and Waters¹³ have expressed the opinion that scopolamine has a definite place in preanesthetic medication. The psychic depression produced by scopolamine in contrast to the stimula-

9 Lehman, G., and Knoefel, P. K. A Pharmacologic Study of Trichlorethanol, *Am J M Sc* **197** 638-646, 1939.

10 Molitor, H., and Robinson, H. Studies on the Pharmacological Properties of Trichlorethanol, *Anesth & Analg* **17** 258-263, 1938.

11 Leake, C. D. Chemical Adjuncts to General Anesthesia. *California & West Med* **33** 714-717, 1930.

12 Guedel, A. E. *Inhalation Anesthesia*, New York, The Macmillan Company, 1937.

13 Waters, R. M. Pain Relief for Children, *Am J Surg* **39** 470-475, 1938.

tion produced by atropine plus the effect of scopolamine in counteracting in part, the respiratory depression produced by morphine makes the combination of scopolamine and morphine of definite value.

The dose of atropine sulfate or scopolamine hydrobromide used as a preanesthetic agent (0.3 to 0.65 mg.) has essentially no inhibitory effects on the parasympathetic system except for that portion regulating the secretion from the salivary glands and the mucous glands in the mucosa of the oral and respiratory tracts. There is no paralyzing action on the vagus nerves to the heart with the usual small dose, in fact atropine sulfate or scopolamine hydrobromide in amounts of 0.75 mg. or less actually produces bradycardia in man, as has been shown by McGugan,¹⁴ Harris,¹⁵ Kochman¹⁶ and Platz.¹⁷ This bradycardia is due apparently to the effect of these agents in stimulating the medullary centers and making the vagovagal reflex more active. When 1 to 2 mg. doses of atropine sulfate or scopolamine hydrobromide are given the paralyzing effect on the peripheral endings of the vagi predominates, and one obtains a marked increase in the heart rate, but even with these large doses there is a preliminary reduction of the heart rate in man, as was shown by Sturgis and his associates.¹⁸ In experiments by Baxter and me¹⁹ it was observed that when atropine sulfate or scopolamine hydrobromide was given to dogs in small amounts (0.5 mg. or less) after administration of morphine, the heart rate was decreased, and auriculo-ventricular block of varying degree occurred. One may be certain, then, that the amount of either of these two drugs usually employed clinically as a preanesthetic medicament has little or no effect as far as paralyzing the cardiac branches of the vagus nerves is concerned.

If the general anesthetic agent is to be such a substance as nitrogen monoxide or ethylene, which does not irritate the upper respiratory tract and thus does not cause an increase in salivary and mucous secretion,²⁰ there is little value in the use of atropine or scopolamine as a pre-

14 McGugan, H. The Effect of Small Doses of Atropin on the Heart Rate. *J. A. M. A.* **76** 1338-1340 (May 14) 1921.

15 Harris, I. The Action of Digitalis and Atropine on the Peripheral Blood Pressure, *Lancet* **1** 1072-1074, 1921.

16 Kochman, M. Beiträge zur Wirkung des Scopolamin HBr, *Arch. internat. de pharmacodyn. et de therap.* **12** 90-128, 1904.

17 Platz, O. Wirkung des Atropins auf Puls und Blutdruck, *Ztschr. f. d. ges. exper. Med.* **28** 81-89, 1922.

18 Sturgis, C. C., Wearn, J. T., and Tompkins, E. H. Effects of the Injection of Atropine on the Pulse Rate, Blood Pressure and Basal Metabolism in Cases of Effort Syndrome, *Am. J. M. Sc.* **158** 496-502, 1919.

19 Robbins, B. H., and Baxter, J. H., Jr. Unpublished data.

20 Robbins, B. H. Effects of Various Anesthetics on Salivary Secretion. *J. Pharmacol. & Exper. Therap.* **54** 426-432 1935.

anesthetic agent²¹ When ether, which has been shown to depress the vagovagal reflex,²² is given the paralytic action of atropine on the vagus nerves to the heart is not necessary, but its use is essential for its effect in reducing the secretion of the salivary and mucous glands

The high frequency of cardiac irregularities present during chloroform anesthesia is the reason for using atropine, as has been stated by Leake,¹¹ but the quantity necessary for paralysis of the vagus nerves is far greater than the amount usually employed

When cyclopropane is to be used, either atropine sulfate or scopolamine hydrobromide should be administered to reduce the secretions of the upper respiratory tract It is well known that bradycardia and ventricular escape (extrasystole) are frequently observed during cyclopropane anesthesia, and the use of atropine sulfate or scopolamine hydrobromide to prevent these changes would seem to be indicated, but here again the dose would have to be much larger than the usual 0.3 to 0.65 mg In many experimental studies by Seevers and his associates,³ Meek and his associates²³ and Baxter and me,²⁴ it has been shown that deep anesthesia in dogs can be maintained with cyclopropane without the development of abnormal changes in the heart as shown by electrocardiographic records, but Baxter, Fitzhugh and I²⁵ have shown that as soon as one uses morphine as a preanesthetic medicament bradycardia and ventricular escape are observed in practically all planes of anesthesia produced by cyclopropane, this is attributed to a combined action of morphine and cyclopropane on the vagus system²⁶ These

21 Clement, F W Nitrous Oxide-Oxygen Anesthesia, Philadelphia, Lea & Febiger, 1939

22 Shafer, G D, Underwood, F J, and Gaynor, E P The Action of Amytal in Impairing Vagus Cardiac Inhibitory Effects, *Am J Physiol* **91** 461-466, 1930

23 Meek, W J, Hathaway, H R, and Orth, O S Effects of Ether, Chloroform and Cyclopropane on Cardiac Automaticity, *J Pharmacol & Exper Therap* **61** 240-252, 1937

24 Robbins, B H, and Baxter, J H, Jr Studies of Cyclopropane III The Relation of Electrocardiographic Changes to the Arterial Concentrations of Oxygen, Carbon Dioxide and Cyclopropane in Dogs Anesthetized with Cyclopropane, *J Pharmacol & Exper Therap* **61** 162-174, 1937

25 Robbins, B H, Baxter, J H, Jr, and Fitzhugh, O H Studies of Cyclopropane The Use of Barbiturates in Preventing Cardiac Irregularities Under Cyclopropane or Morphine and Cyclopropane Anesthesia, *Ann Surg* **110** 84-93, 1939 Robbins, B H, and Baxter, J H, Jr Studies of Cyclopropane VIII The Effect of Premedication with Morphine or Amytal upon the Heart Rate, Rhythm and Blood Pressure in Dogs Under Cyclopropane Anesthesia *J Pharmacol & Exper Therap* **68** 85-95, 1940

26 Robbins, B H, Fitzhugh, O G, and Baxter, J H, Jr Studies of Cyclopropane VII An Analysis of the Factors Controlling the Heart Rate in Dogs Anesthetized with Cyclopropane or Ether After Premedication with Morphine, *J Pharmacol & Exper Therap* **66** 206-215, 1939, Action of Morphine in Slowing the Pulse, *ibid* **66** 216-223, 1939

irregularities can be abolished by large doses of atropine or scopolamine, but with small doses the bradycardia and auriculoventricular block are increased. These irregularities may be abolished by small doses of amytal, which has been shown to decrease vagal activity. For these reasons as well as others, Baxter, Fitzhugh and I²⁵ have suggested that a barbiturate should replace morphine as the main preanesthetic agent when cyclopropane is to be used. This suggestion, derived from experimental studies with dogs, has been supported clinically, as was reported in the *Lancet*,²⁷ in which, in a discussion of the aforementioned report it was stated: "These experiments will confirm a practice that has already been adopted, on empirical grounds, by a good many of the anesthetists who have had wide experience of cyclopropane."

Rovenstine and Cullen,²⁸ in discussing the anesthetic management of patients with a hyperactive carotid sinus reflex, stated that barbiturates (evipal, pernoston, pentothal) depress or abolish the effect of the carotid sinus reflex on the heart. Weiss and Baker²⁹ have shown that atropine in amounts sufficient to release the heart from the normal vagal tone also prevents cardiac slowing in patients with a hyperactive carotid sinus reflex but that phenobarbital in relatively large doses has no such effect.

The relation of mechanical irritation of the upper respiratory tract to reflex changes in the heart has been investigated by Reid and Brace.³⁰ They found that introduction of a tracheal catheter as well as inflation of the Waters-Guedel cuff frequently led to cardiac irregularities as shown by electrocardiographic records, and they attributed these cardiac changes to the vagovagal reflex. Although they stated that cyclopropane anesthesia frequently produces cardiac irregularities, those produced by mechanical manipulation in the trachea may occur when nitrogen monoxide or nitrogen monoxide and ether are being used. Since morphine increases vagal tone, they advised that atropine should be given together with the morphine to abolish the reflex inhibition of the heart. In this relation Weiss and Ferris³¹ showed that a dose of atropine sulfate of 1.5 mg. was necessary to abolish this type of vagovagal effect on the heart.

27 Morphine or Barbiturates Before Cyclopropane? Annotations, *Lancet* 2 704, 1939

28 Rovenstine, E. A., and Cullen, S. C. The Anesthetic Management of Patients with a Hyperactive Carotid Sinus Reflex, *Surgery* 6 167-176, 1939

29 Weiss, S., and Baker, J. P. The Carotid Sinus Reflex in Health and Disease, *Medicine* 12 297-354, 1933

30 Reid, L. C., and Brace, D. E. Irritation of the Respiratory Tract and Its Effect upon the Heart, *Surg., Gynec. & Obst.* 70 157-162, 1940

31 Weiss, S., and Ferris, E. B. Adams-Stokes Syndrome with Transient Complete Heart Block of Vago-Vagal Reflex Origin, *Arch. Int. Med.* 54 931-951 (Dec.) 1934

In discussing ventricular fibrillation in relation to anesthesia and preanesthetic medication, Guedel and Knoefel³² pointed out that hyperactivity of the sympathetic system and the increased output of epinephrine are factors which predispose to ventricular fibrillation, and, since morphine not only does not depress the sympathetic system but actually causes an increase in epinephrine output, this agent should be supplanted by barbiturates, which depress the sympathetic nervous system in addition to producing sedation.

CORRECTIVES IN LOCAL AND SPINAL ANESTHESIA

In patients who are to have operative procedures carried out with the operative region under spinal, paravertebral or local anesthesia, a preliminary dose of morphine or of a barbiturate is of value in giving the patient mental or psychic relief before as well as during the operation. The dose and time of administration should be about the same as for medication preceding use of a general anesthetic.

With spinal anesthesia or paravertebral block a marked fall in blood pressure is frequently encountered, due to paralysis of the sympathetic nerves with subsequent pooling of blood in the arterioles and capillaries, which in turn leads to a stagnant anoxia, as has been shown by Shaw and his associates³³. In order to counteract this effect one of the longer-acting sympathomimetic amines should be injected some fifteen minutes before the beginning of spinal or paravertebral anesthesia. Ephedrine has been employed most widely for this purpose and has been found very satisfactory.

After preanesthetic medication with barbiturates, Tatum and his associates³⁴ and Knoefel and his co-workers³⁵ found that animals require two to four times as much cocaine or procaine hydrochloride to produce toxic manifestations as did animals to which barbiturates were not administered. This observation would indicate that premedication with barbiturates may be of value in preventing toxic manifestations due to absorption of local anesthetics during surgical procedures in man.

32 Guedel, A. E., and Knoefel, P. K. Ventricular Fibrillation in Anesthesia, *Am J Surg* **34** 496-499, 1936.

33 Shaw, J. L., Steele, B. F., and Lamb, C. A. Effect of Anesthesia on Blood Oxygen. Study of Effect of Spinal Anesthesia on Oxygen in Arterial and Venous Blood, *Arch Surg* **35** 503-511 (Sept.) 1937.

34 Tatum, A. L., Atkinson, A. J., and Collins, K. H. Acute Cocaine Poisoning, Its Prophylaxis and Treatment in Laboratory Animals, *J Pharmacol & Exper Therap* **26** 325-335, 1925.

35 Knoefel, P. K., Herwick, R. P., and Lovenhart, A. S. The Prevention of Acute Intoxication from Local Anesthetics, *J Pharmacol & Exper Therap* **39** 397-411, 1930.

The observation of Meek and Seevers³⁶ that barbiturate premedication protects against the cardiac irregularities produced by ephedrine is a factor supporting the use of barbiturates for patients who are to receive ephedrine to prevent the fall in blood pressure during spinal anesthesia.

If the recent observations on rabbits by Cunningham and Bieter,³⁷ who reported that substituting an equimolar solution of calcium chloride and magnesium chloride for 30 per cent of the sodium chloride solution used to dissolve procaine hydrochloride for spinal anesthesia causes an increase in duration of sensory anesthesia of 800 per cent and in duration of motor anesthesia of 200 per cent in animals without any signs of irritation, are found to obtain in man, a further step in increasing the safety of spinal anesthesia will have been taken.

PREANESTHETIC MEDICATION IN RELATION TO ANOXIA

The present concept of anoxia as divided into four types, anoxic, anemic, stagnant and histotoxic, may be discussed briefly in relation to preanesthetic medication.

Anoxic Anoxia—There is some evidence that preanesthetic medication gives rise to slight anoxic anoxia. Data on the oxygen saturation of arterial blood from dogs after administration of morphine, as reported by Blalock,³⁸ show that there is a reduction of saturation of 3 to 4 per cent and that when administration of morphine is followed by ether anesthesia there is a further decrease of 3 to 15 per cent in the oxygen saturation of the arterial blood, depending in part on the depth of anesthesia.

More recently McClure and his associates³⁹ have reported that in man after preanesthetic medication with seconal or cyclopal there is a decrease of 5 to 20 per cent in oxygen saturation of arterial blood, after avertin with amylene hydrate, 70 to 90 mg per kilogram, a reduction of 2 to 20 per cent, and after spinal anesthesia following morphine or seconal premedication, a reduction of only 1 to 10 per cent. Likewise, in dogs which receive full anesthetic doses of evipal there is a reduction of 15 per cent, with seconal a reduction of 15 per cent, with pentobarbital a reduction of 25 per cent, with amytal a reduction of 10 to 25 per cent, with dial a reduction of 7 to 8 per cent, and with avertin with amylene hydrate a reduction of 12 per cent.

36 Meek, W. J. and Seevers, M. H. The Cardiac Irregularities Produced by Ephedrine and a Protective Action of Sodium Barbitol, *J. Pharmacol. & Exper. Therap.* **51** 287-307, 1934.

37 Cunningham, R. L. and Bieter, R. N. Experiments on the Potentiation of Procaine Spinal Anesthesia in the Rabbit. *J. Pharmacol. & Exper. Therap.* **66** 410-422, 1939.

38 Blalock, A. Cardiac Output in Dogs During Ether Anesthesia. *Arch. Surg.* **14** 732-751 (March), 921-933 (April), 978-990 (May) 1927.

39 McClure, R. D., Hartman, F. W., Schneider, I. G. and Schell, J. A. Anoxia, *Ann. Surg.* **110** 835-850, 1939.

These studies, together with others, would indicate that when morphine, avertin or a barbiturate is given in moderate to full anesthetic doses anoxic anoxia may follow

Anemic Anoxia—Searles⁴⁰ has shown that amytal in full anesthetic doses in dogs usually produces a reduction of the hematocrit, hemoglobin and red cell values of some 20 per cent, due to the sedimentation of red cells in the spleen. If similar results are found in man with small doses of barbiturates (amytal), then it might be considered that barbiturates produce anemic anoxia

Stagnant Anoxia—Shaw and his co-workers³³ have shown that spinal anesthesia produces stagnant anoxia and that the use of vasoconstrictor drugs which act principally on the capillary walls should be employed to prevent this condition

Histotoxic Anoxia—In discussing the relation of preanesthetic medication to anoxia, McClure and his associates³⁹ stated "Narcotics, particularly morphine and barbiturate derivatives in moderate to large doses, tend to produce anoxia, especially of the histotoxic type" This conclusion is based on their own work and on the publications of Quastel and Wheatley,⁴¹ Jowett and Quastel⁴² and Jowett⁴³

They (McClure and his associates³⁹) presented two tables (I and X) showing the decrease in oxygen uptake of brain tissue (slices) apparently removed from the animal (species not given) after administration of barbiturates, morphine or avertin with amylene hydrate. The data in these tables are interpreted as showing that these agents produce histotoxic anoxia, but because of the lack of descriptive information in the text it is impossible to evaluate them properly

Jowett and Quastel,⁴² using a concentration of evipal of 0.033 per cent on tissue from the guinea pig, found that the increased oxygen uptake after addition of dextrose to the Warburg cup was 33 per cent less than in the control brain tissue, whereas the same concentration of evipal reduced the oxygen uptake of the spleen, testis and slices of liver only 17, 16 and 2 per cent respectively. This concentration of evipal (0.033 per cent) is three to four times the concentration found by Kennedy⁴⁴ to kill the normal guinea pig. A concentration of 0.016

40 Searles, P. W. The Effect of Ether and Sodium Amytal Anesthesia on the Blood, *Am J Surg* **41** 399-404, 1938

41 Quastel, J. H., and Wheatley, A. H. M. Narcosis and Oxidations of the Brain, *Proc Roy Soc, London, s B* **112** 60-79, 1932, Narcotics and Brain Oxidations. Reversibility of Narcotic Action in Vitro, *Biochem J* **28** 1521-1529, 1934

42 Jowett, M., and Quastel, J. H. Effects of Narcotics on Tissue Oxidation, *Biochem J* **31** 565-578, 1937

43 Jowett, M. The Action of Narcotics on Brain Respiration, *J Physiol* **92** 322-335, 1938

44 Kennedy, W. P. Sodium Salt of C-C-Cyclohexenyl-Methyl-N-Methyl Barbituric Acid (Evipan) Anesthesia in Laboratory Animals, *J Pharmacol & Exper Therap* **50** 347-353, 1934

per cent of evipal reduced the oxygen uptake by 10 per cent, but again this is three times the dose which will produce anesthesia of sixty minutes duration in the guinea pig

Quastel and Wheatley,⁴¹ in studying the effect of phenobarbital, barbital and chloral hydrate in 0.12 per cent concentration in vitro (four to eight times the fatal dose in vivo), found a reduction of oxygen uptake after dextrose was added of 20 to 94 per cent, but when 0.12 per cent ethyl carbamate (urethane) or paraldehyde 0.12 per cent was added in vitro (an approximate anesthetic concentration in vivo) the oxygen uptake was reduced only 17 and 3 per cent respectively

Wortis,⁴⁵ using the Barcroft-Warburg technic, found that morphine sulfate added to brain tissue in vitro (32 and 8 mg per hundred cubic centimeters) caused no reduction in oxygen uptake or respiratory quotient. Phenobarbital of 0.5 per cent concentration in the cup (thirty times the anesthetic concentration in vivo) produced a marked reduction of oxygen uptake both before and after the addition of dextrose

When brain tissue was removed from rats and cats after administration of full anesthetic doses of amytal or butylbromallylbarbiturate or 120 mg of morphine sulfate per kilogram and the oxygen uptake was followed for two hours or more, Wortis⁴⁵ found no significant difference in rate of oxidation between the tissues from animals receiving drugs and those from control animals. The addition of dextrose to the cup did not bring out any difference between the tissue from the medicated and that from the control animals

Groce and Pierce⁴⁶ found that when morphine sulfate was given to rats (50 mg per hundred grams) and the brain tissue removed one hour later the rate of oxygen uptake when dextrose was added at the beginning of the experiment was identical in the tissue obtained from the morphine-treated and that from the control rats. When no dextrose was added to the cup the rate of oxygen uptake was greater in tissue from morphine-medicated rats than in that from control rats, this is explained by the fact that morphine produces an increase in dextrose in the blood, so that the tissue from the rats which received morphine had a greater reserve of dextrose than the brain tissue from control rats

Likewise, Schudeman and Seevers⁴⁷ found that the rate of oxygen uptake of minced brain from the rat was the same in the cup containing

⁴⁵ Wortis, S. B. Respiratory Metabolism of Excised Brain Tissue. II. The Effects of Some Drugs on Brain Oxidation, *Arch Neurol & Psychiat* **33** 1022-1029 (May) 1935

⁴⁶ Groce, E. C., and Pierce, I. H. Effect of Morphine on the Oxygen Consumption of Brain Tissue in the Rat, *J Pharmacol & Exper Therap* **53** 156-168, 1935

⁴⁷ Schudeman, F. E., and Seevers, M. H. Some Effects of Morphine on the Respiration of Brain, Spinal Cord and Skeletal Muscle in Vitro, *J Pharmacol & Exper Therap*, to be published

morphine as in the control cup. The addition of pyruvate or dextrose failed to bring out any significant depressing effect of morphine on the oxidation of the brain.

The data in the literature at present show that the preanesthetic drugs morphine, barbiturates and avertin in amylene hydrate when added to brain tissue in relatively very high doses, will inhibit in part the increase in extra oxygen uptake in the presence of added substrate, particularly dextrose (the data of Schideman and Seevers are excepted). When, however, morphine or a barbiturate is used to produce deep anesthesia in animals and then the brain tissue studied for oxygen uptake there are few or no convincing data indicating that these agents alter the utilization of oxygen by the brain tissue. With these observations in mind it is difficult to see how the use of morphine or a barbiturate as a preanesthetic agent gives rise to the histotoxic type of anoxia.

SUMMARY

The general custom of administering nonvolatile chemical agents, *i. e.*, morphine, barbiturates or avertin with amylene hydrate, to produce depression of the central nervous system in patients before the induction of anesthesia is based on sound principles. The type and amount of such agents administered vary from patient to patient, depending on the individual characteristics of the patient as well as on the anesthetic agent to be employed. Preanesthetic sedation must, therefore, be individualized.

The use of special agents, *i. e.*, atropine, scopolamine, barbiturates or ephedrine, to prevent or counteract undesirable side reactions due to the effect of the anesthetic is of special value in maintaining the anesthetized subject in the best possible condition. These special agents have been discussed in relation to the effects they produce on the different tissues of the body.

The subject of anoxia in relation to preanesthetic sedation has been discussed. Anoxic anoxia may result from respiratory depression when large doses of morphine, barbiturates or avertin with amylene hydrate are given. Anemic anoxia may possibly result from premedication with amytal. Stagnant anoxia as a result of spinal anesthesia may be prevented by the use of ephedrine.

There is little or no evidence that the preanesthetic sedatives when used in ordinary amounts cause anoxia of the histotoxic type.

The judicious use of preanesthetic agents, both adjuvants and correctives, should be of great value to the anesthetist in reducing the number of undesirable changes occurring during anesthesia.

PREOPERATIVE AND POSTOPERATIVE TREATMENT OF THE PATIENT WITH DIABETES

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In this discussion we shall presuppose an understanding of the handicaps of the diabetic patient in addition to his carbohydrate intolerance. We refer to the high incidence of arteriosclerosis, particularly in the coronary vessels and the vessels of the kidneys, the susceptibility to and seriousness of infection both in the field of operation and in the urinary tract, the effect of prolonged or acute sepsis on the diabetic state, and the frequency with which pressure of little consequence to the non-diabetic patient, may result in an area of necrosis, particularly on the heels and over the sacrum.

We also assume a careful evaluation and treatment of the patient's general condition, with particular reference to his state of nutrition and any vitamin or other deficiency which may exist.

PREOPERATIVE TREATMENT

Operations of Election—It is our aim, in general, to send the diabetic patient to the operating room well fed, with the liver well stocked with glycogen and with the urine showing no acid and little or no sugar.

Controlled Diabetes The diabetic patient under treatment who, on an adequate diet, controls his diabetes with or without the aid of insulin needs little special preparation for operation. Such a patient spends never less than forty-eight hours but rarely more than seventy-two hours in the hospital prior to operation unless the nature of the proposed surgical procedure requires a longer period of preparation.

The preoperative diet should be rather more simple than the coarse food which such a patient is probably accustomed to taking.

Insulin is given in amounts comparable to the patient's usual requirement though probably in smaller doses and more frequently. If the patient is taking regular insulin, no attempt is made to change to protamine zinc insulin before operation, although protamine zinc insulin given on the morning of operation, by virtue of its long-continued action, gives excellent protection during the operative period. One half to two thirds of the usual dose of insulin should be given on the morning of operation.

From the New England Deaconess Hospital

Among 193 diabetic patients recently operated on at the New England Deaconess Hospital, 79 took protamine zinc insulin alone, 79 took regular insulin combined with protamine zinc insulin, 27 took regular insulin only and 8 were taking no insulin before operation. At their discharge, 103 of these patients were taking protamine zinc insulin only (one dose a day), 65 were taking one dose of protamine zinc insulin and one dose of regular insulin, the average amount being 12 units of crystalline insulin and 40 units of protamine zinc insulin, and 23 patients continued taking crystalline insulin only. Two patients were taking no insulin at discharge.

It was formerly our custom to give nourishing fluids to within four hours of operation. Experience showed, however, that in many instances fluid was still in the stomach at the time of operation and that it could not be depended on to increase the glycogen reserve. The practice was therefore discontinued, and now no nourishing liquids are given within twelve hours of operation. A fluid intake to assure an output of at least 1,500 cc per day should be given. If necessary, parenteral fluids in the form of physiologic solution of sodium chloride with or without 5 per cent dextrose, depending on the carbohydrate need, are given. We do not routinely give either hypodermoclysis or intravenous fluid on the morning of operation before the patient goes to the operating room unless there is some specific indication for it.

Untreated or Uncontrolled Diabetes. If the diabetic patient has not been undergoing dietary treatment, a sufficiently long period of preparation should be undertaken to assure proper nourishment before an operation of election is done. Any sudden and rapid restriction of diet, especially of the carbohydrates, may result in disaster. Acidosis, disturbances of hepatic function and even anuria have been so produced. Ten patients who recently underwent amputation of a leg had an average diet during the days preceding operation of 140 Gm of carbohydrate, 68 Gm of protein (the equivalent of 0.8 Gm per kilogram of body weight) and fat to a total of 1,555 calories, or an average of 23 calories per kilogram of body weight. The untreated patient should be given protamine zinc insulin supplemented by regular insulin as needed. If a patient has been under treatment for a long time and is reasonably well controlled on a diet the proportions of which are not just what one might wish, changes in diet should be made very gradually.

Emergency Operations.—It is important neither to delay a necessary operation nor, in the presence of infection, to use massive doses of insulin to render the urine free of sugar before operation is undertaken. If time permits, the urine should be rendered free of diacetic acid. If, on the other hand, the urgency of the surgical condition is such as to necessitate immediate operation, the surgeon must recognize the increased

hazards of operation and the limitations placed on the magnitude and extent of the operative procedure as well as on the use of ether anesthesia. Such operations not only greatly increase the difficulties of controlling the diabetic state but are done on patients whose resistance to trauma and infection is below that which can be obtained by more deliberate preparation.

POSTOPERATIVE TREATMENT

Diet and Fluid—It is customary to give each patient 1,500 cc of 2.5 per cent dextrose in physiologic solution of sodium chloride by hypodermoclysis promptly on his return from the operating room. One thousand to 1,500 cc of 5 per cent dextrose in physiologic solution of sodium chloride is given intravenously in the late afternoon or early evening of the same day. Thereafter the total fluid intake is 3,000 to 4,000 cc daily. It is hoped to maintain an output of 1,500 cc or more of urine daily. However, because we have seen elderly patients who at necropsy have showed edema of the lungs, we hesitate to give larger quantities of fluids to our older patients with questionable cardiac reserve. Unless there is a chloride deficiency or loss of chloride by diarrhea, vomiting or excessive perspiration, we rarely give more than 30 Gm of salt in a fluid administered parenterally.

Except when the nature of the operation requires special dietary regulations, liquids, such as oatmeal gruel made with water, hot tea or coffee (with crackers or toast) are given freely, and ginger ale and orange juice with egg white are given sparingly on the day after operation. On the second postoperative day milk and, if the patient desires, cooked cereals, junket or boiled custard are added to the diet. Thereafter the diet is increased according to the patient's tolerance and desires. If possible, 100 to 150 Gm of carbohydrate is given daily, any amount not taken by mouth being supplied by parenteral administration in the form of 5 per cent dextrose by vein or 2.5 per cent dextrose in physiologic solution of sodium chloride under the skin. Occasionally as much as 300 Gm of carbohydrate may be given in cases of severe damage to the liver. Eventually a diet approximating 160 Gm of carbohydrate, 75 Gm of protein and 90 Gm of fat will be attained. This represents the average diet on discharge of 10 patients after amputation of a leg for gangrene.

Insulin—The availability of two types of insulin, the rapidly acting crystalline insulin and the more slowly acting protamine zinc insulin, provides two means of controlling glycosuria and acidosis. These drugs are so potent that their dangers as well as their great advantages at the time of operation must be fully understood.

Insulin reactions due to hypoglycemia present a real danger unless nurses, house officers and the physician in charge are prepared to

recognize and treat them properly. The characteristic sudden weakness, hunger, nervousness, sweating and pallor occurring three to four hours after the giving of the rapidly acting insulin or twenty-two to twenty-four hours after administration of protamine zinc insulin should be easily recognized. On the other hand, certain symptoms may be masked by other symptoms or, indeed, may be absent in the patient whose clinical picture is complicated by some surgical condition. Almost any mental change, from nervousness to actual unconsciousness, convulsions or a maniacal state, may occur, and the physician's first thought when any unusual symptoms appear in the diabetic patient who has taken insulin should be the necessity for diagnosis of possible hypoglycemia by an immediate examination of the level of blood sugar. A venous infusion of 10 per cent dextrose may be started at once and may be continued or discontinued, depending on the level of blood sugar.

It is important to recognize that it is much easier to avoid diabetic coma than insulin shock, that normal repair of the wound will take place with a decreasing amount of sugar in the urine even though the blood sugar level may be as high as 180 or 200 mg per hundred cubic centimeters for four or five days after operation and that therefore no attempt need be made to render the urine free of sugar during the first three or four days of the postoperative course.

Our usual postoperative insulin routine is as follows: (1) test the urine (Benedict's test) every four hours and (2) give insulin (crystalline), 15 units if the reaction is red, 10 units if it is yellow and 5 units if it is yellow-green.

As soon as the patient can take his usual amount of food, the dose of protamine zinc insulin may be returned to its preoperative level, with addition of crystalline insulin in accordance with the results of the test. During the convalescence, when the urine becomes free of sugar it may be desirable to test the need for insulin by omitting or reducing a single dose, usually the noon dose first. Determinations of the value for blood sugar should be made as soon as the urine becomes free of sugar, as a safeguard against hypoglycemic reaction.

COMMENT

Paralysis of the bladder, particularly in elderly diabetic patients, is by no means uncommon and is often without symptoms. In the case of such a patient, therefore, the result of a test of urine not obtained by catheter may not represent the true excretion of sugar at that time but rather that in the accumulated urine of some hours before. A red reaction thus may lead to unnecessary administration of insulin and serious hypoglycemia.

Patients with active acute infectious processes which may go on for days, for example carbuncles or infections of the extremities, may require increase of the dose of insulin to as much as 100 to 150 units per day. Then, suddenly, after drainage of the carbuncle or amputation of the limb, the patient's tolerance may rapidly improve, with the result that if the high dose has been continued serious hypoglycemia will occur. For this reason it is our practice in surgical conditions such as these not only to make a quantitative determination of the concentration of sugar in the twenty-four hour specimen of urine but, in addition, to test single specimens at two-hour intervals during the day, so that a continuous picture of the sugar excretion is obtained. Thus if the patient suddenly begins to excrete specimens free of sugar the dose of insulin can be immediately omitted.

The administration of dextrose solution intravenously as a means of feeding the diabetic patient after operation is of great value, but hypoglycemia develops easily if insulin is administered at the same time as the dextrose. Also, if insulin is administered according to the amount of sugar in the first urine voided after administration of intravenous dextrose, hypoglycemic reaction will frequently occur. A good practice is to give a small dose of insulin, depending on the amount of sugar in the urine just before dextrose is given intravenously. No insulin is given in an attempt to utilize the dextrose about to be administered. The patient is encouraged to void two hours after the injection has been completed. The urine will in all probability contain a large amount of sugar. If insulin is given depending on the amount of sugar contained in this specimen, the level of blood sugar may be falling in response to the stimulation produced by the dextrose solution, and the insulin will then provoke serious hypoglycemia. If any subsequent specimens of urine contain sugar however, the usual order for insulin may be safely followed.

SUMMARY

The diabetic patient, in addition to his metabolic disturbance, has many hazards commonly associated with his disease which must be carefully evaluated and, as far as possible, corrected in the preparation of the patient for operation.

A diabetic patient should go to the operating room well nourished with his liver well stocked with glycogen and with the urine free of acid and containing little or no sugar.

The postoperative fluid and dietary routine of the diabetic patient is not unlike that of the nondiabetic surgical patient, particularly during the first four or five days. A carbohydrate intake of from 100 to 150 Gm should be maintained by parenteral administration of dextrose if the patient is not able to take it by mouth.

Insulin is given (depending on the urinary excretion of sugar) in small amounts and frequently. Hypoglycemic reactions are more difficult to avoid when insulin is being given than is acidosis, and all members of the team must be constantly alert so as to assure an early diagnosis and prompt treatment. The parietic bladder, the rapid gain in tolerance following removal or drainage of infected areas and attempts to utilize all of the sugar given in intravenous infusion represent some of the more common causes of insulin reaction.

PREOPERATIVE AND POSTOPERATIVE CARE OF PATIENTS WITH LESIONS OF THE STOMACH AND OF THE DUODENUM

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The principles that underlie the preoperative preparation of patients who have lesions of the stomach and of the duodenum are concerned for the most part with attempts to facilitate compensation for the effects of obstruction with its associated metabolic disturbances, such as dehydration and avitaminosis, and with anemia due to hemorrhage. Although these principles are applicable in the main to the preparation of patients for operation, they apply equally well when like conditions develop postoperatively. However, the appearance of such conditions subsequent to operation fortunately is of infrequent occurrence. Although the principles of preoperative therapy directed toward control of physiologic chemical changes are similar to those of postoperative treatment, the patient's response to the acute phases of postoperative complications may be more severe, with a much greater general systemic reaction than the response to some chronic phase that exists prior to operation. In the latter instance there is usually sufficient time, if proper treatment is forthcoming, for the patient's physiologic processes to compensate for some of the effects of the disease.

PREOPERATIVE CARE

Obstruction—The most frequent lesion that produces obstruction of the stomach and duodenum is chronic duodenal ulcer. In many cases, gastric ulcers of the lesser curvature of the stomach may produce sufficient disturbance of gastric motility to lead to pylorospasm and to an obstruction of a considerable degree. Malignant lesions of the lower third of the stomach not infrequently produce varying degrees of obstruction.

Whatever the cause, such obstructing lesions produce considerable metabolic and chemical changes as the result of inability of solid food to pass the point of obstruction and probably allow absorption of products of delayed and altered proteolysis, thus, various degrees of avitaminosis

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and states of nutritional deficiency develop. The inability of fluids sufficient to meet the bodily requirement to pass the obstructed region and the loss of gastric secretion with its acid and chloride, when present, result in various degrees of alkalosis and hypochloremia. The last-mentioned changes may occur as the result of toxemia due to dehydration even in the absence of vomiting. These toxic factors were called to our attention in 1923 by the classic experiments of Haden and Orr¹ and by the clinical report of Brown, Eusterman, Hartman and Rowntree.² Recently, Peters,³ in discussing metabolic disorders associated with gastrointestinal disease, called attention to the reduction of the level of sodium in cases of pyloric obstruction, expressing the belief that this has a greater significance than reduction of the level of chloride or of that of bicarbonate because the concentration of sodium does not suffer until a considerable degree of dehydration has occurred. Compensation for the toxemia of dehydration with alkalosis, hypochloremia and loss of sodium by intravenous administration of solutions of sodium chloride with and without dextrose has been a routine in the preoperative preparation of patients who have gastric or duodenal obstruction with retention of more than 300 cc of gastric contents.

The need for treatment depends not on the amount of gastric contents retained when the study is made but on the alteration of blood chemistry coincidental with the obstruction. We feel that the toxic state is determined by the degree of persistency of the obstruction. Intermittent obstruction—even complete obstruction occurring intermittently—is not likely to permit severe toxic avitaminosis or a state of nutritional deficiency to develop. Patients with intermittent obstruction usually are sent into the hospital a few days prior to operation, they receive intravenous injections of physiologic solution of sodium chloride and of dextrose solutions. The amount of each that is necessary is dependent on the requirements of the individual patient for establishment of a proper fluid balance and a normal acid base equilibrium, which includes restoration of the blood chlorides to a normal level. This is possible in cases in which such treatment is not contraindicated by the presence of some associated complicating condition, such as diabetes or cardiac

1 Haden, R. L., and Orr, T. G. The Cause of Certain Acute Symptoms Following Gastro-Enterostomy, *Bull. Johns Hopkins Hosp.* **34** 26-30 (Jan.) 1923.

2 Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G. Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany, *Arch. Int. Med.* **32** 425-455 (Sept.) 1923.

3 Peters, J. J. Metabolic Disorders in Gastrointestinal Disease, *Rev. Gastroenterol.* **6** 84-90 (March-April) 1939, abstracted, Dick, G. F., and others. *Year Book of General Medicine*, Chicago, The Year Book Publishers, Inc., 1939, pp. 783-787.

incompetency, which of itself is not severe enough to contraindicate operation on the stomach. Usually, two injections of 1,000 cc of a solution that contains 10 per cent dextrose and 0.9 per cent sodium chloride every twenty-four hours effectively meets these requirements, one injection is given early in the morning, and the other, late in the afternoon. Administration of too much sodium chloride manifests itself by an elevation of the level of blood chlorides beyond normal values and occasionally by the development of edema of the ankles and hands. Injection of an isotonic solution of 5 per cent dextrose without the sodium chloride is an effective method of administering fluid intravenously and assists in maintaining a proper amount of fluid. Dextrose, of course, has definite caloric value. We prefer to administer the intravenous solutions by intermittent injection rather than continuously, as the latter method becomes tiresome to the patient and may produce thrombosis of the vein.

The patient is given a diet, the fluid state of which is determined by his individual needs. When the degree of obstruction is severe the fluidity of the diet should be increased. Some patients with incomplete obstruction of long standing, which may lead to a severe toxic state, can tolerate and actually need a more varied intake of food than can be obtained by means of liquids alone, even if the liquid diet is augmented by supplementary vitamins. The stomach is emptied twice daily (or more frequently if necessary) by gastric aspiration by means of a small Sawyer tube passed through the nose or mouth into the stomach. Removal of retained secretions from the stomach allows it to return to a reasonably normal size and assists in restoration of tone to the gastric wall. Thus, the surgical procedure on the stomach is much easier and gastric motility returns more quickly after the operation. The liquid diet administered should be palatable and should contain sufficient vitamins, if it does not, vitamin B and vitamin C should be given. Vitamin K should be given if there is a prothrombin deficiency or if there is evidence of hepatic insufficiency, as the liver, under the strain of prolonged operation, may prove inadequate for its role in maintaining normal coagulability of the blood.

Determination of the concentration of blood urea, blood chlorides, serum proteins and carbon dioxide-combining power at the start of the period of preparation, with repetition of the studies after two or three days, serves to indicate whether the toxemia due to dehydration has been controlled.

Anemia—One or more transfusions will be required prior to operation if anemia is extreme. On the other hand we have been particularly impressed with the fact that patients with moderate degrees of anemia seem to stand operative procedures in a satisfactory manner. A patient

who has a concentration of hemoglobin of less than 40 per cent (6 Gm) and less than 2,500,000 erythrocytes per cubic millimeter benefits from a preoperative blood transfusion. Although it is of some advantage to give such a transfusion two or three days before the operation, we have not hesitated to give it on the day preceding the operation or, if urgent surgical treatment is required, during the operation and subsequently. In 1 case, of extremely serious bleeding from a perforating, obstructing hemorrhagic duodenal ulcer, two transfusions were given prior to operation because the erythrocytes numbered 1,960,000 per cubic millimeter and the concentration of hemoglobin was 32 per cent (4.9 Gm). At operation, on Oct. 27, 1939, the extent of the lesion and the condition of the patient precluded any procedure other than gastroenterostomy. Twelve transfusions were given subsequent to operation, over a period of four weeks. Although on one occasion (November 4) the concentration of hemoglobin reached the low level of 17.8 per cent (2.7 Gm) and the erythrocytes numbered 890,000 per cubic millimeter, with the passing of time healing of the ulcer occurred and bleeding ceased. On November 19 the hemoglobin level had risen to 75.9 per cent (11.5 Gm), and the erythrocytes numbered 3,570,000 per cubic millimeter. Bleeding from the ulcer had ceased, and the patient made an excellent recovery.

In another case of acute bleeding from a duodenal ulcer, transfusions totaling 3,600 cc of blood were given prior to partial gastrectomy for a subacute perforating hemorrhagic duodenal ulcer. The patient recovered satisfactorily from the operative procedures and has been well and free of bleeding since.⁴

We have found it of advantage whenever transfusion is contemplated to determine the blood groups of the patient's relatives and to test their blood by means of the complement fixation test to determine whether syphilitic infection is present and whether they may be used as donors if necessary. This helps to decrease the expense of treatment and, in addition, prevents depletion of the blood bank. The efficiency of the properly controlled blood bank as a reservoir for blood is well known.

Perforation—The patient with acute perforation of a duodenal ulcer usually requires an immediate operation, a part of which, at least, is closure of the perforation. In such a case it is advantageous to empty the stomach with a stomach tube before operation, this is particularly advisable if a general anesthetic is to be used.

The patient who has a subacute perforation complicating the gastric or duodenal lesion can be made a safer surgical risk and the technical

4 Herrell, W. E. Prolonged Transfusion and Immediate Partial Gastrectomy for Hemorrhagic Duodenal Ulcer. Report of Case, Proc. Staff Meet., Mayo Clin. 13: 261-263 (April 27) 1938.

difficulties of the operation may be simplified by medical treatment of the inflammatory process and by simultaneous symptomatic treatment of the primary lesion. Inflammation occurs within the lesion itself, but more important and at times crucial is the dispersion of the inflammatory process to contiguous and adjacent tissues. This may occur when the lesions are in the stage of penetration, when an acute perforation is walled off, with formation of an abdominal mass that at times is palpable through the abdominal wall, and when chronic and sub-acute perforations occur with local peritoneal irritation. The treatment for the inflammation is like that used for any inflammatory abdominal process, that is, "splinting" as far as is possible through rest in bed and sedation as needed, application of cold locally, omission of violent purgation, cleansing of the bowel by bland enemas and relief of symptoms when possible through a diet planned according to the individual needs. A smooth diet of low or increased residue, a high caloric or high vitamin diet, a non-acid-producing diet, a liquid diet and similar diets all are used to obtain symptomatic relief of discomfort from alkalis, together with supplementary feeding and vitamins when indicated. During the preparatory period, pain is relieved by sedatives and opiates if necessary. The patient should have sufficient rest at night, and usually one of the barbiturates serves as an effective hypnotic. Masses, due to inflammation, which may be palpable through the abdomen melt away under such proper therapy in five to six days and have been observed to disappear to such an extent by the time surgical exploration is carried out that only slight evidence remains. Less extensive inflammation also responds to such therapy. The surgeon's work is made easier, and the patient's resistance to infection is not taxed so much after preoperative treatment. Also, peritonitis is less likely to occur. However, unless the patient has been forewarned, relief from pain and improvement in his general condition may lead him to suspect that the ulcer has healed and that a surgical procedure is not necessary.

POSTOPERATIVE CARE

The postoperative care of the patient may be considered from the standpoint of routine measures to be instituted in cases in which no complication exists and from the standpoint of treatment of postoperative complications.

General Measures—A general measure of importance is maintenance of a positive fluid balance so that intake exceeds output or so that a positive fluid balance of at least 1,000 cc every twenty-four hours or, better, 1,500 to 1,800 cc, exists. Administration of fluid by proctoclysis is still an easy and effective method of administering fluids parenterally, but it gives the surgeon less assurance that the patient

actually has the fluid than do the intravenous or the more painful subcutaneous methods. It is possible to administer as much as 1,800 cc by proctoclysis each twenty-four hours, usually without discomfort to the patient. This may be supplemented by subcutaneous injections of physiologic solution of sodium chloride, usually introduced in the subpectoral region, the needles being placed usually in the areolar tissue beneath the breast but sometimes in the subcutaneous tissue on the inner aspect of the thigh. An injection of 0.5 per cent procaine hydrochloride in the region in which the needle is to be inserted for the hypodermoclysis frequently assists in reducing pain to a minimum, especially if the fluid is not forced into the tissues by pressure but is allowed to enter by means of gravity alone at a rate near that at which it is absorbed.

Intravenous injections of a 10 per cent solution of dextrose in physiologic solution of sodium chloride are used to supplement the other methods of administration of fluid. In selection of the constituents of the fluid in respect to the relation of the concentration of dextrose to that of sodium chloride, the principles previously described in the section on preoperative care are followed.

In the absence of retention of gastric contents the patient is allowed $\frac{1}{2}$ ounce (15 cc) of water each hour, beginning forty-eight hours after operation, this is increased to 1 ounce (30 cc) an hour on the following day (fourth postoperative day). A small quantity of milk is then allowed at frequent intervals, to which are added thin gruel and custard until about the twelfth or thirteenth day, when the patient is allowed a soft diet. In from six weeks to three months a reasonably general diet is permitted. It has been our experience that there is a greater tendency on the part of the nursing staff and dietitians to overfeed patients than to underfeed them. This is true particularly between the tenth and the twentieth day. We think that this may account for some of the retentions occasionally seen in that period of convalescence.

Fluid Output—It is important to observe the output of urine and the specific gravity each day, for a low output may mean insufficient fluid intake or retention of urine. If the former seems adequate even in the absence of ability to palpate a distended bladder, we feel it advisable to catheterize the patient after voiding to eliminate the possibility that residual urine is present. If it is present, the patient is catheterized intermittently every eight hours until it disappears. At times use of a retention catheter is the better procedure.

If retention of gastric contents in amounts of not more than 800 to 1,000 cc during a twenty-four hour period is present, intermittent emptying of the stomach by aspiration may satisfactorily tide the patient over the period of retention. This is usually less uncomfortable and tedious to the patient than is continuous suction. The latter is advisable

in cases of retention when the retained contents exceed 800 to 1,000 cc in twenty-four hours, in which case it serves not only to keep the stomach empty but to produce less discomfort for the patient than that caused by a distended stomach. Clark and his associates⁵ have called attention to the fact that in cases of stasis of the upper portion of the gastrointestinal canal, when it is necessary to aspirate the gastric and intestinal contents continuously over a long period, the patient in the meantime taking a very limited amount of food, a deficiency of prothrombin may develop and hemorrhage occur. This has been noted in a few instances and is promptly relieved by parenteral administration of the antihemorrhagic naphthoquinone derivatives that have vitamin K activity.

A careful record should be kept of the amount of fluid removed from the stomach in order to maintain a positive fluid balance. The color of the fluid is important, for if the fluid contains a large quantity of bile it means that the anastomotic opening between the proximal loop of jejunum and the stomach is open, whereas that between the stomach and the distal loop of jejunum is not.

Laboratory Studies—We find it advantageous to have a routine urinalysis made on the second or third day following operation. This furnishes a good indication of the ability of the patient's kidneys to concentrate urine, indicates the presence or absence of infection of the urinary tract and immediately calls attention to the presence of unsuspected diabetes. A routine examination of the blood is made at the same time. Such examinations have revealed that even among patients who appear to have lost a minimum of blood during a surgical procedure a variable degree of anemia is present after a major operation. If the content of hemoglobin is less than 8 Gm and the number of erythrocytes is less than 3,000,000 per cubic millimeter, we consider a blood transfusion indicated. If gastric retention is present, analyses of the blood for concentration of urea and chlorides and carbon dioxide-combining power are made every third day. If abnormal changes in these constituents of more than an average degree exist, appropriate measures to compensate for them by replacement therapy are immediately instituted. These studies of the blood are repeated as frequently as seems necessary to determine whether sufficient fluids and electrolytes are being administered.

Pulmonary Complications—Pulmonary complications subsequent to operation usually consist of atelectasis, bronchopneumonia or pulmonary

⁵ Clark, R. L., Jr., Dixon, C. F., Butt, H. R., and Snell, A. M. Deficiency of Prothrombin Associated with Various Intestinal Disorders. Its Treatment with the Antihemorrhagic Vitamin (Vitamin K), *Proc. Staff Meet., Mayo Clin.* **14**: 407-416 (June 28) 1939.

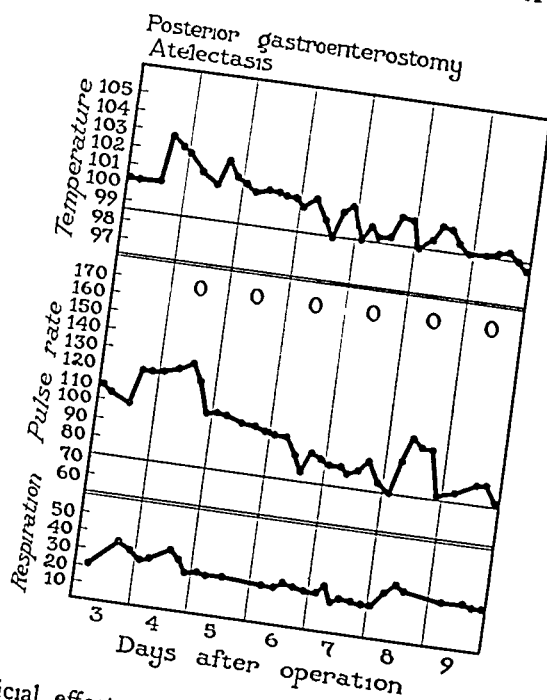


Fig 1—Beneficial effect of oxygen on increased temperature and pulse rates resulting from atelectasis



Fig 2—Early roentgen appearance of massive atelectasis of the right lung

embolism Although it might be felt that atelectasis would occur more frequently after general anesthesia, experience has shown that it occurs probably with as great a frequency after spinal anesthesia Since in some cases of spinal anesthesia supplementary anesthetic gases and oxygen are given, the same factors conducive to pulmonary embolism might be brought into play as though no spinal anesthetic had been given

Atelectasis is to be suspected when the patient's temperature, pulse rate and respiratory rate increase progressively after operation (fig 1) Physical signs of the collapse can frequently be elicited a few hours after the operation, but roentgen examination is the most accurate method of determining its presence (fig 2) The patient should be placed immediately on the side corresponding to the undisturbed lung and

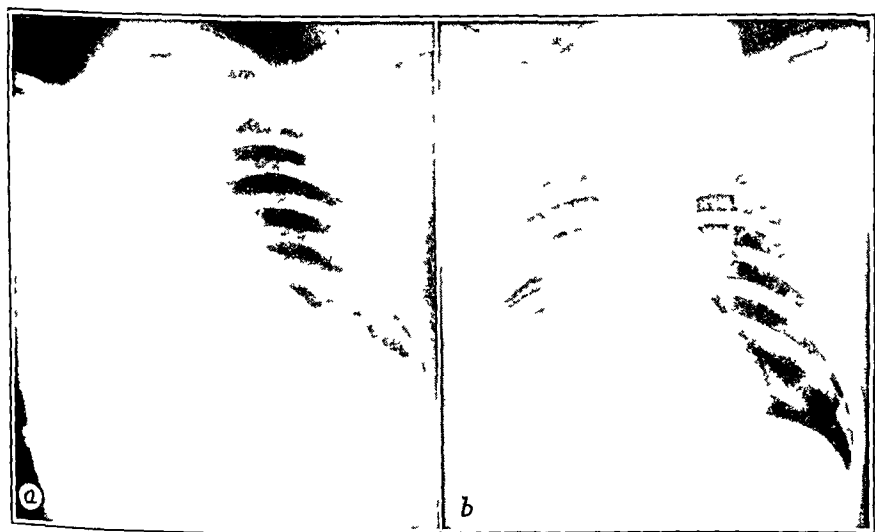


Fig 3—Atelectasis of the right lung, *a*, three days after onset, with evidence of some air in the upper lobe, *b*, eight days after onset, with evidence of air in the upper and middle lobes

should be changed frequently from his back to this position In this fashion and by encouraging him to cough one hopes to dislodge the plug of mucus that obstructs the bronchus (fig 3) Placing a hand on each side of the patient's thorax and compressing it when he starts to cough are helpful in expelling mucus from the bronchi Inhalations of carbon dioxide and oxygen (95 per cent oxygen and 5 per cent carbon dioxide) after a short time at frequent intervals increase the depth of expiratory excursion and assist, first, in dislodging a plug of mucus and, second in inflating the collapsed portion of the lung Oxygen is particularly valuable in such cases, as it decreases the respiratory rate and helps the patient to expel the bronchial mucus In the oxygen tent the temperature and pulse rate decrease more rapidly than

elsewhere, and as restlessness and anxiety are decreased the patient has a greater feeling of comfort. We prefer to administer oxygen in an oxygen tent rather than through an oxygen mask. Secretions from the respiratory tract may accumulate in the mask, producing considerable annoyance to the patient. When these methods have failed, several patients have been subjected to bronchoscopic procedures, with excellent results (fig 4). Experience has shown that it is advisable to reduce the use of opiates to a minimum so as not to inhibit the coughing reflex. When necessary, the barbiturates serve as good sedatives to obtain rest and sleep.

Usually the patient has passed the stage of acute reaction from the atelectasis in thirty-six hours, and the oxygen can then be gradually

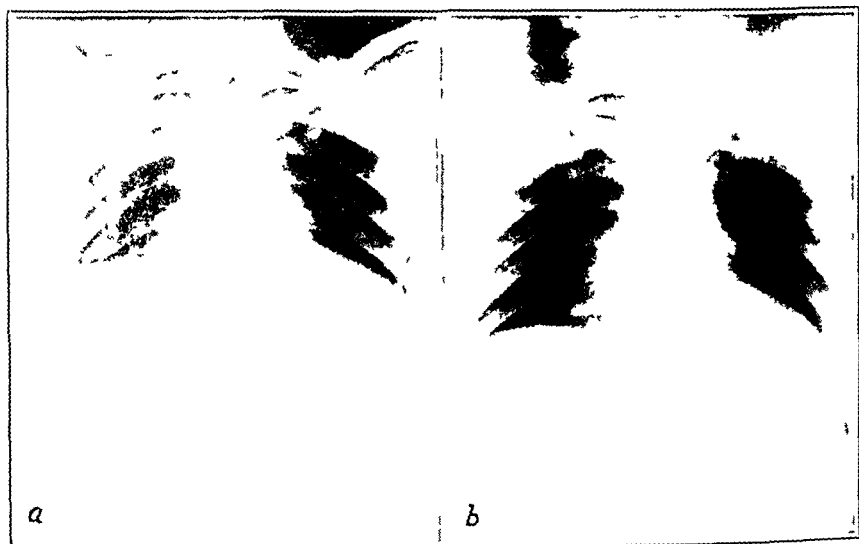


Fig 4—Roentgen appearance of (a) atelectasis of the lower lobe of the right lung and (b) disappearance of atelectasis after removal of mucus from the bronchus of this lobe by the bronchoscope. Although atelectasis occurred in this patient after cholecystectomy on Dec 15, 1939, the clinical picture of atelectasis appearing the next day, with marked response to removal of the obstructing mucus from the bronchus by means of the bronchoscope on December 17, was so typical and striking that the case is mentioned here in spite of the fact that the condition did not follow an operation on the stomach or on the duodenum.

withdrawn, first for half an hour and then for increasing periods, as the patient's condition warrants.

Bronchopneumonia. There is some evidence to suggest that many cases of suspected bronchopneumonia are, in reality, cases in which pulmonary infarction has occurred or cases of infections grafted on regions affected by atelectasis (figs 5 and 6). Whether this is true or not, the fact remains that a rapid and remarkable response is obtained

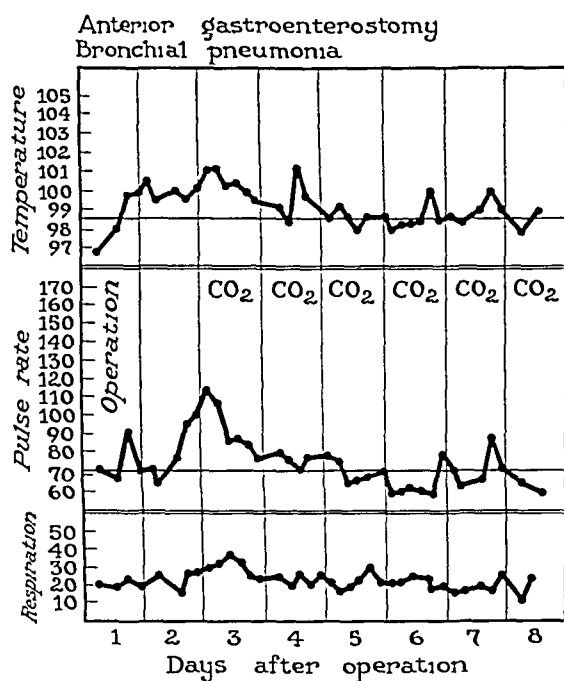


Fig 5—Effect of administration of carbon dioxide to a patient who had bronchopneumonia following an anterior gastroenterostomy

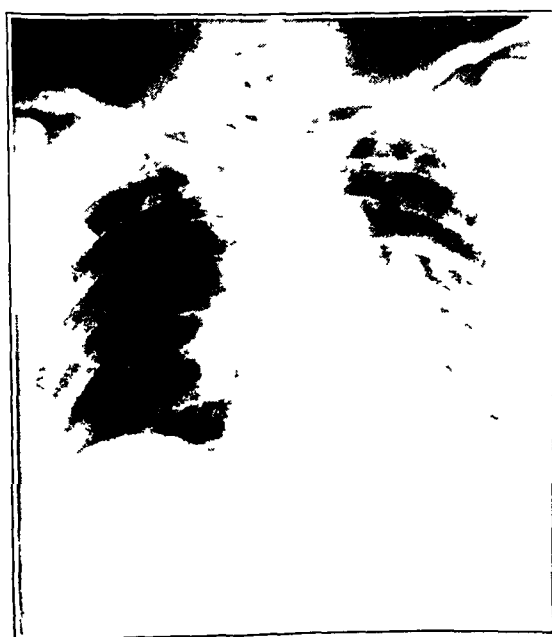


Fig 6—Increased density indicative of bronchopneumonia in the lower lobes of both lungs (same patient as in figure 5)

in such cases by administration of sulfanilamide, sulfapyridine or sulfamethylthiazole. Although in cases of pneumonia we formerly typed the patient's sputum and used specific rabbit serum (and still do in suitable cases), the rapid response to chemotherapy has decreased the use of specific serums in such cases in our experience practically to the vanishing point. Clinical experience has proved that when bronchopneumonia is suspected from the increased temperature and pulse rate, even in the absence of positive thoracic or roentgen findings, the patient does better if immediately placed in the oxygen tent. If signs of bronchopneumonia can be elicited on physical examination and demonstrated by roentgen examination and if the patient's condition warrants, chemotherapy should be started without delay (figs 7 and 8). With sulfanilamide, it was our custom to give an initial dose of 75 grains (5 Gm) in the first twenty-four hours, following it with doses of 40 to 60 grains (2.6 to 4 Gm) in each succeeding twenty-four hours for five or six days. At no time should the concentration of sulfanilamide in the blood be allowed to exceed 15 mg per hundred cubic centimeters. With the introduction of sulfapyridine, Moersch⁶ and Hinshaw⁷ advocated administering 60 to 90 grains (4 to 6 Gm) of this drug in the first four hours, then 15 grains (1 Gm) every four hours, continuing for five to six days (figs 9 and 10). If it is necessary to institute chemotherapy in the first forty-eight hours subsequent to operation, when the patient is not taking fluids orally, the sodium salt of sulfapyridine is given intravenously, 0.06 Gm per kilogram of body weight is given, and the dose is repeated every six to eight hours. Estimations of the concentration of these substances in the blood are made at frequent intervals to prevent overdosage. Reexaminations of the blood should be made to eliminate too great a drop in the number of leukocytes, and repeated examinations of the thorax, particularly roentgen examinations, are made to eliminate the possibility that fluid (especially pus) has developed in the pleural cavity. In our experience such complications are extremely rare.

Pulmonary Embolus In 828 operations on the stomach and on the duodenum performed at the Mayo Clinic in 1938, the incidence of fatal pulmonary embolism was 0.6 per cent. This is a significant figure when one takes into account that with patients who fail to recover from operation permission for postmortem examination is obtained and autopsy is carried out in 80 per cent of the cases. Various methods of reducing the incidence of fatal pulmonary embolism have been attempted and carried out, among which are the standardized frequent moving

6 Moersch, H. J. Personal communication to the authors.

7 Hinshaw, H. C. Chemotherapy in Pneumonia, Proc. Staff Meet., Mayo Clin. 14: 769-772 (Dec. 6) 1939.

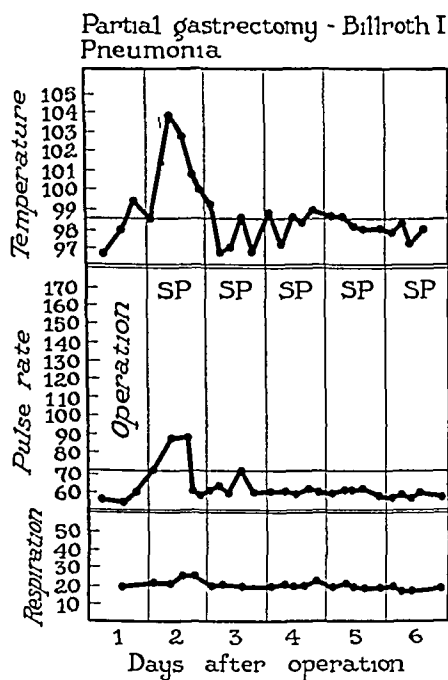


Fig 7—Effect of sulfapyridine on the temperature and pulse rate of a patient who had pneumonia after a partial gastrectomy with a Billroth I anastomosis for carcinoma of the stomach

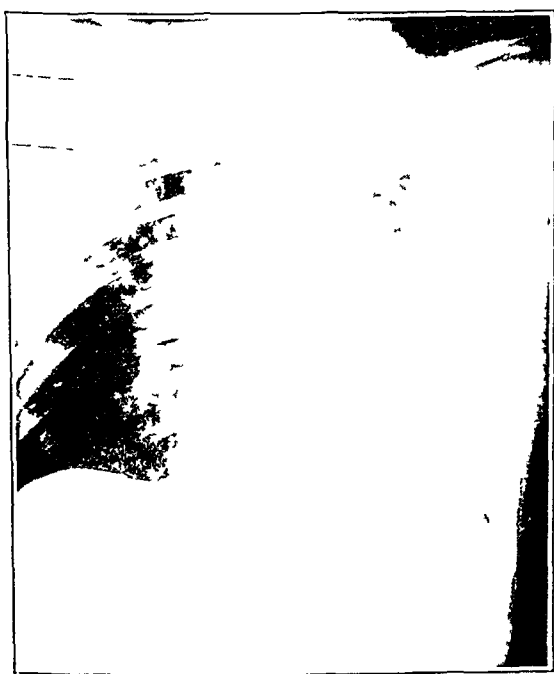


Fig 8—Consolidation in the lower lobe of the left lung and resolving pneumonia in the upper lobe of the right lung

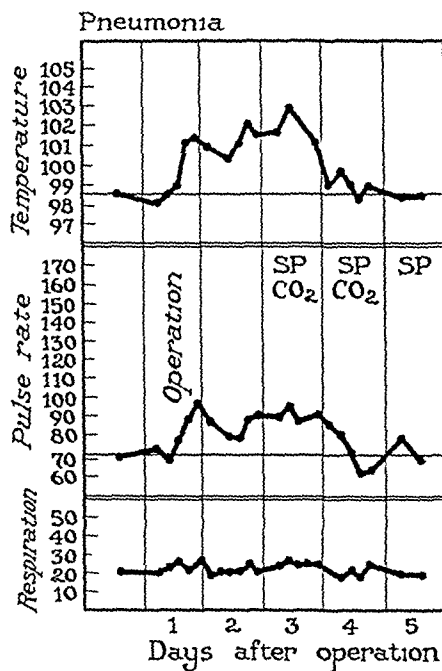


Fig 9—Record of the temperature and pulse of a patient who had pneumonia postoperatively and who was treated with sulfapyridine and inhalations of carbon dioxide

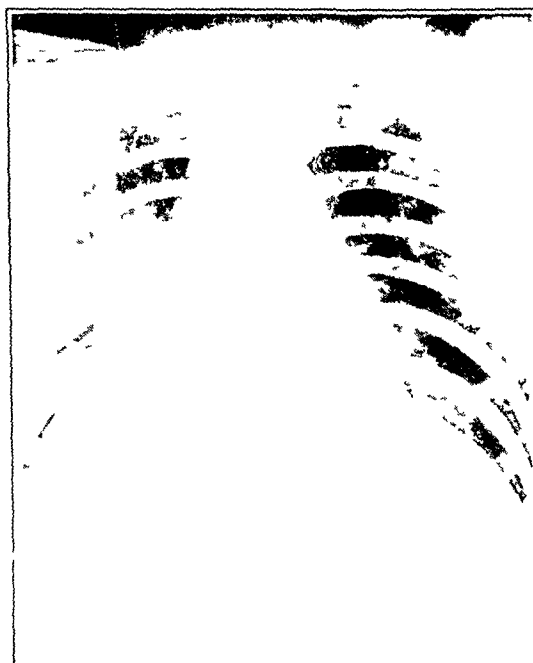


Fig 10—Infiltration of the hilus of the right lung in radial distribution toward the periphery of the lung, with a shift of the mediastinum toward the right, indicative of pneumonia or infarction

of the patient from side to side elevation of the foot of the bed administration of thyroid extract and more recently intravenous use of purified heparin. Although in large series of cases these various methods have been used to decrease the incidence of postoperative fatal embolism (and all of the methods have value) the fact remains that fatal pulmonary embolism continues to occur. Fortunately, however, it is infrequent and presents it would seem one of the few problems remaining unsolved in the treatment of postoperative complications. Intravenous injections of heparin at present seem to justify the expense entailed although further use of this preparation may show it to have deleterious effects. It should not be accepted as a standard medicament as yet. The heparin that we have received for use in these cases has been supplied through

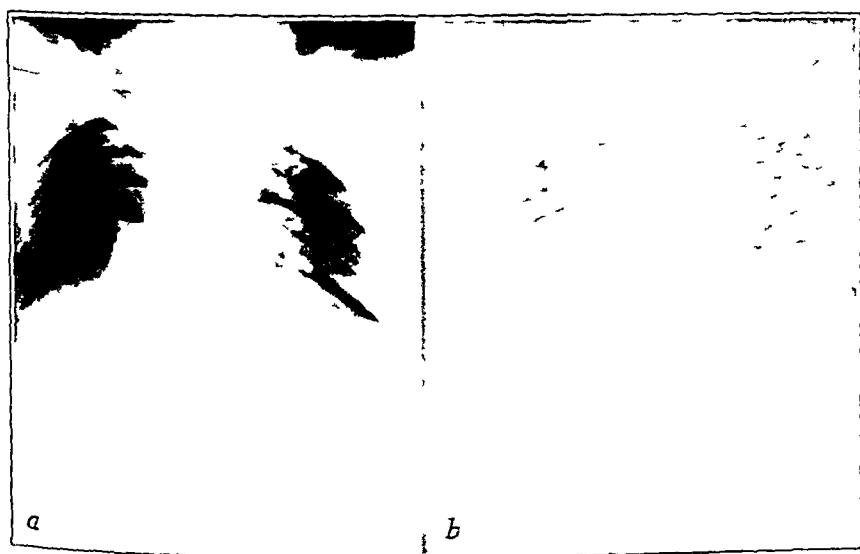


Fig 11—Roentgen evidence of (a) infiltration of the lower lobe of the right lung and (b) an infarct of the right lung (four days later)

the cooperation of Dr Charles H. Best, from the Connaught Laboratories at the University of Toronto, Toronto, Canada. Following the suggestions for the clinical use of heparin made by Murray and his associates⁸ at the Toronto General Hospital, Priestley and Essex⁹ instituted its use at the Mayo Clinic in certain selected cases. A detailed report of the results is under preparation by Priestley at present. From the preliminary clinical trial it seems as though this treatment may be of definite value to certain patients with thrombosis and embolism. The following case is in point:

⁸ Murray, D. W. G., Jacques, L. B., Perret, T. S. and Best, C. H. Heparin and the Thrombosis of Veins Following Injury, *Surgery* 2: 163-187 (Aug.) 1937.
⁹ Priestley, J. T. and Essex, H. E. Unpublished data.

REPORT OF A CASE

A man aged 52, heavily built and weighing 200 pounds (90.7 Kg), was operated on Dec 12, 1939. Cholecystectomy was performed for subacute cholecystitis with cholelithiasis. Convalescence was normal until the twelfth day after operation, when thrombophlebitis of the right internal saphenous vein developed. There was comparatively severe tenderness along the course of the vein, and the associated pain required codeine sulfate for relief. The pain extended into the right groin. On January 3 a pulmonary embolus lodged in the lower lobe of the right lung and produced a pulmonary infarct (fig 11, *a* and *b*) with the characteristic signs and symptoms, this was confirmed by roentgen examination on

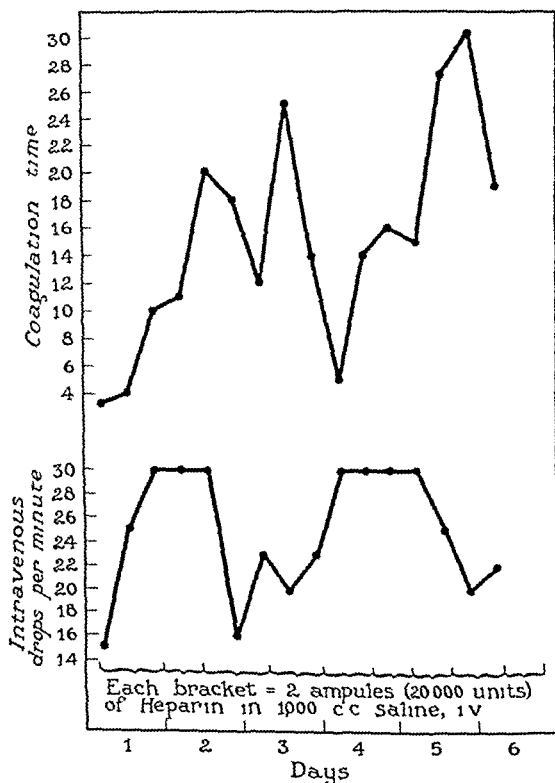


Fig 12—Increase in coagulation time of the blood associated with continuous intravenous administration of heparin

Jan 4, 1940 The temperature and the pulse rate increased from January 2 to 5. Intravenous injections of heparin were started on January 5, and heparin was administered continuously for nine days. The rate of injection was sufficient to maintain a coagulation time two to three times that which existed before treatment (fig 12). Two hours after the injection was started the pain in the patient's right leg decreased noticeably, and his general condition improved. His temperature and pulse became normal on January 11, seven days after the start of the injection of heparin. The injection was discontinued on January 13. He was dismissed from the hospital on January 17. Residual edema in the lower portion of the right leg was compensated for by application of a rubber elastic bandage.

Postoperative Gastrointestinal Obstruction—There are two types of obstruction that may occur in the vicinity of the anastomosis subsequent to operation, the most frequent being edematous narrowing of the gastroenteric stoma, resulting either from inflammation at the stoma itself or from inflammation in the edematous upper mesocolon adjacent to it (if the anastomosis has been made posterior to the colon). Of rare occurrence is mechanical obstruction of noninflammatory origin such as that resulting from pulling of the loops of jejunum back up the anastomosis into the lesser peritoneal cavity or from the pulling of loops of small intestine behind the site of anastomosis, between the posterior abdominal wall. Obstructions resulting from inflammatory changes described usually do not manifest themselves until the sixth or seventh postoperative day. In rare instances gastric retention may occur two and a half to three weeks postoperatively. The patient feels on discovering the delayed retention and the relief which the patient experiences from adequate emptying of the stomach is so dramatic as to be clearly remembered by both the surgeon and the patient. Such retention results from overfeeding and has no sequelae when gastric atony is corrected.

The retention which begins on the sixth or the seventh postoperative day is a different story. The patient who has been taking several hundred cubic centimeters of fluid, including nourishment, begins to regurgitate small amounts of it or has a feeling of uncomfortable fulness in the abdomen which may be associated with an increase in pulse rate and a decrease in temperature. Unless the stomach is emptied by means of a tube, vomiting may occur, the vomitus usually contains variable amounts of bile. Retention of a few hundred to many hundred cubic centimeters of gastric contents is noted from day to day.

The mechanical obstructions usually manifest themselves immediately after operation, the patient retaining large amounts of gastric contents from the beginning. Should the obstruction be mechanical in origin the sooner operation and relief of the obstruction are carried out the better. Usually minor measures are all that is necessary to correct the obstruction, such as pulling the anastomosis down into its proper position below the opening in the transverse section of the mesocolon and anchoring it there by sutures. Most inflammatory obstructions subside spontaneously, although if they last beyond the sixteenth or the seventeenth postoperative day some method of supplying nourishment into the gastrointestinal tract usually is advisable. This is most easily done by performance of a temporary jejunostomy¹⁰ and no 18 F or no 20 F catheter is introduced into the jejunum approximately 20 to 30 cm

¹⁰ Wesson, H. R. Postoperative Gastric Retention Treated by Jejunostomy for Feeding. Proc. Staff Meet., Mayo Clin. 12: 747-751 (Nov. 24) 1917.

distal to the site of jejunal anastomosis with the stomach, and the end of the catheter is directed downward. Nourishment immediately can be introduced into the intestine in this fashion, and sufficient calories, with the proper ratio of protein, fat and carbohydrate, may be given to maintain the patient in physiologic balance until the inflammatory obstruction subsides, which it may not do until the twenty-fifth to the twenty-eighth day following the initial anastomosis. In a few cases one of us (W W) has known the stomach to fail to empty completely through the anastomosis for thirty-six days¹¹

It is, of course, necessary to compensate for the loss of gastric secretion by giving fluids either intravenously or subcutaneously. A positive fluid balance of intake over output of at least 1,000 cc should be maintained. An intravenous solution of 10 per cent dextrose in physiologic solution of sodium chloride or an approximately isotonic solution of 5 per cent dextrose is effective for restoring the electrolytes of the blood and the acid base equilibrium to normal levels, the isotonic 5 per cent dextrose solution being used in place of the 10 per cent dextrose and physiologic sodium chloride solution when the level of blood chlorides has returned to normal and when evidence of retention of chloride, such as edema of the lower extremities and the hands, manifests itself.

In some cases of mechanical obstruction at the stoma, one of us (W W) has used two catheters instead of one, inserting them in the jejunum closer to the anastomosis and directing the second catheter upward through the anastomosis into the stomach to eliminate the necessity of intermittent or continuous gastric aspiration through a nasally or orally introduced stomach tube. On a few occasions he has made a small opening in the stomach and has passed a no. 20 F or a no. 22 F catheter through it and through the stoma into the distal loop of jejunum, burying the catheter for 1 inch (2.5 cm) or so in the wall of the stomach after the method of a Witzel gastrostomy. This permits introduction of fluids and nourishment into the jejunum, and the tube through the stoma apparently acts as a drain, for the gastric fluids pass along it into the jejunum. If catheters used in this fashion are passed through an opening in the gastrocolic omentum before they are brought to the outside of the body, after their removal omentum will plug the opening which the jejunostomy tube occupied, and leakage of gastric or intestinal fluids will not occur.

Experience has shown that when the patient is sufficiently obese the transverse section of the mesocolon is impregnated with fat or is shortened to such an extent that it cannot be accurately sutured above the stoma. This is the type of case in which gastric retention is likely to develop. When operation is again performed in such a case, a brawny,

11 Chauncey, L. R. Unpublished data.

edematous induration of the transverse section of the mesocolon is noted. In such cases we believe that this, rather than edema of the site of anastomosis itself, is usually the cause of the gastric stasis. To prevent such a possibility, anastomosis of the jejunum to the stomach can be made anterior to the colon. The increased amount of fat in the gastrocolic omentum and the enlarged fatty transverse section of mesocolon which bulges the transverse section of the colon forward make it necessary in an anastomosis anterior to the colon to use a longer proximal loop of jejunum than is used in an anastomosis posterior to the colon. In some cases of anterior anastomosis stasis develops in the proximal loop of jejunum, which may necessitate an enteroanastomosis between the proximal and the distal loop of jejunum on the twelfth to the sixteenth day to relieve retention. If the loop of jejunum used in making an anastomosis anterior to the colon is comparatively long retention is more likely to occur.

In many cases in which pyloric obstruction prevents proper intake of nourishment and fluids prior to operation and the patient is in a state of malnutrition, a catheter introduced into the stomach through the nose or mouth is carried through the stoma of the anastomosis at the time the anastomosis is made and is placed in the distal loop of jejunum (or in the duodenum if an operation of the Billroth I type is performed) so that feedings can be begun immediately after operation. This is of particular value in cases of long-standing pyloric obstruction in which partial gastric atony has occurred and efficient emptying of the stomach therefore is delayed postoperatively.

Equally effective and much more pleasant for the patient is the performance of a temporary jejunostomy and insertion of a tube at the time of the initial operation on the stomach, for through the tube both fluids and nourishment can be introduced directly into the intestine without the discomfort of the indwelling nasal tube. Recently Stengel and Ravdin¹² have suggested the use of a two-way tube swallowed into the stomach, the end of the shorter tube being placed in the stomach at the time of operation to remove accumulating gastric secretion and the distal tube being pushed down into the jejunum for feeding purposes. The tube in the jejunum is used for introduction of nourishment and fluids that have a high content of amino acids in this way the plasma proteins are maintained at a reasonably normal level and thus increase in the edema of the anastomosis which Ravdin has shown experimentally to occur in subjects with low levels of plasma proteins is prevented.

12 Stengel, A. Jr. and Ravdin, I. S. The Maintenance of Nutrition in Surgical Patients with a Description of the Orogastric Method. *Annals of Surgery* 6: 511-519 (Oct.) 1939.

Recent studies by Chauncey¹¹ on the relation of the concentration of serum protein to postoperative gastric retention have shown that hypoproteinemia is not the sole causative agent in the production of gastric retention. Indeed, in the appearance, maintenance or disappearance of gastric retention he has found that the concentration of serum protein does not consistently play an important part. He admitted, however, that in cases of severe hypoproteinemia with general manifestations gastric retention may occur.

Jejunostomy Formula in Use at Present

	Day on Which Diet Is Employed					
	1st	2d	3d	4th	5th	6th
Total cc per hour	30	30	60	60	90	90
Total cc per day	720	720	1,440	1,440	2,160	2,160
Ingredients						
Ice cream mix,* Gm	150	200	400	450	700	800
Skim milk powder, Gm		25	50	60	75	75
Eggs			1	2	3	3
Dextrose, Gm	25	25	60	60	80	100
Ascorbic acid, mg			25	50	50	50
Halibut liver oil, drops				15	15	15
Thiamin chloride, mg			3	5	5	5
Water cc	570	520	990	890	1,310	1,210
Composition						
Carbohydrate	47	65	139	150	213	245
Protein	6	15	36	46	67	71
Fat	21	30	66	79	121	135
Calories	401	590	1,294	1,495	2,209	2,491

* Ice cream mix as used in making ice creams in most institutions is a combination of whole milk powder, cream or butter fat, egg powder and gelatin (carbohydrate, 15 Gm, protein, 4 Gm, fat, 14 Gm). The mix is homogenized and has been more successfully used in making the formula than the milk and cream mixture formerly employed. More normal stools result in cases in which it has been used. Method of preparation: Mix skim milk powder with water to make a smooth paste. Add the remainder of the water specified for that particular formula, dextrose and ice cream mix. Beat the eggs, add halibut liver oil, and beat again. Combine these mixtures, strain and add dissolved ascorbic acid and thiamin chloride. Individual feedings should be warmed to body temperature in hot water before administering.

We have been using a formula which has a composition of 15 Gm of carbohydrates, 4 Gm of protein and 14 Gm of fat (see accompanying table). Most ice cream mixtures contain constituents in this proportion and are made up of whole milk powder, cream or butter fat, egg powder and gelatin. The mix is homogenized and has been more successfully employed in making a formula for use in a jejunostomy tube than has a mixture of milk and cream formerly used, which occasionally produced some diarrhea. More normal stools have resulted in cases in which the ice cream formula has been used. To the mixture are added concentrates of vitamin K, ascorbic acid, halibut liver oil and thiamin chloride (see table).

PREOPERATIVE AND POSTOPERATIVE TREATMENT OF PATIENTS WITH LESIONS OF THE SMALL INTESTINE AND OF THE COLON

JOHN R PAINE, M D
MINNEAPOLIS

The lesions of the small intestine and of the colon which are amenable to surgical treatment may be classified under three main heads. These are (1) inflammatory lesions, such as appendicitis, regional enteritis, diverticulitis and ulcerative colitis, (2) obstructive lesions, which may be taken to include the various pathologic types of obstruction, both partial and complete and both simple and strangulated, and (3) neoplasms not producing obstructive symptoms, such as adenocarcinomas, fibrosarcomas, carcinoids, leiomyomas and occasionally lymphoblastomas. It is important to recognize some such classification as this in any general consideration of preoperative and postoperative treatment, since the principles of treatment indicated for all lesions falling in any of the three classes is in many respects the same.

IMPORTANCE OF PREOPERATIVE AND POSTOPERATIVE TREATMENT IN LIGHT OF RECENT DEVELOPMENTS

The results of recent investigation and research have placed an increased responsibility on the surgeon in his treatment of patients both before and after operation. If the newer methods are understood and applied intelligently the hope of improvement or cure by operation can today be offered to more patients, with a greater degree of comfort and safety, than ever before. The outlook of the "poor risk" who has been the victim of malnutrition or chronic loss of blood or both is considerably better than it was ten years ago. Postoperative nausea, vomiting and distention can be prevented. Peritonitis, while still of great concern, has definitely lost some of its terrors.

GENERAL CONDITION OF THE PATIENT

Vitamins—Vitamin B. It has been pointed out by McNealy, Gubler and Taft¹ that diets prescribed for patients with gastrointestinal lesions usually contain an abundance of vitamins A and D but are frequently deficient in vitamins B and C. At present, knowledge con-

From the Department of Surgery, University of Minnesota Medical School.
1. McNealy, R. W., Gubler, J. A., and Taft, E. H. Dietary Deficiencies in Surgical Patients, *Surgery* 6:48, 1939.

cerning vitamin B deficiency is confused, and much of it is conflicting. It is known, however, from the work of Thompson, Ravdin and Frank² that a deficiency in the entire vitamin B complex produces atony of the gastrointestinal tract and delay in gastric emptying. Other signs of this deficiency are said to be anorexia, diarrhea and hypochlorhydria or achlorhydria. In the presence of these symptoms considerable doubt exists as to which portions of the vitamin B complex are lacking. Thiamin chloride (vitamin B₁) and nicotinic acid, however, are thought to be important factors. All patients in the surgical service of the University Hospitals who are suspected of having a vitamin B deficiency are given daily by oral administration or intramuscular injection 10 grains (0.65 Gm.) of thiamin chloride and 100 mg. of nicotinic acid. These substances given in excess produce no deleterious effects.

Vitamin C. It has been known for many years that wounds in patients with scurvy heal slowly and imperfectly. In 1926, Wolbach and Howe³ showed that the histologic basis for the failure of wounds to heal properly in the presence of a vitamin C deficiency lies in inability of the supporting tissues to produce and maintain normal intercellular substances. Much confirmatory work has been done. That of Lanman and Ingalls⁴ and that of Harvey and his collaborators⁵ are particularly significant. The evidence is fairly conclusive that vitamin C deficiency is an important factor in many cases of evisceration, wound disruption and nonunion of intestinal suture lines. Very recently, Holman⁶ has reported that the formation of adequate fibrinous exudates in cases of peritonitis depends in part on an adequate supply of vitamin C. The correction of vitamin C deficiency is, therefore, of great importance for all abdominal operations.

Unlike any of the other vitamins, deficiency in vitamin C can be ascertained accurately by chemical determination of the quantity of ascorbic acid in the blood or in the urine. Since, however, ascorbic acid is harmless in excess it may be given in cases of probable vitamin C deficiency without determining the blood or urinary levels. At the University Hospitals it is customary to give 100 mg. of ascorbic

2 Thompson, W. D., Ravdin, I. S., and Frank, I. L. Effect of Hypoproteinemia on Wound Disruption, *Arch Surg* **36** 500 (March) 1938.

3 Wolbach, S. B., and Howe, P. R. Intercellular Substances in Experimental Scorbute, *Arch Path* **1** 1 (Jan.) 1926.

4 Lanman, T. H., and Ingalls, T. H. Vitamin C Deficiency and Wound Healing. Experimental and Clinical Study, *Ann Surg* **105** 616, 1937.

5 Howes, E. L., Harvey, S. C., and Hewitt, C. Rate of Fibroplasia and Differentiation in Healing of Cutaneous Wounds in Different Species of Animals, *Arch Surg* **38** 934 (May) 1939. Taffel, M., and Harvey, S. C. Effect of Absolute and Partial Vitamin C Deficiency on Healing of Wounds, *Proc Soc Exper Biol & Med* **38** 518-525, 1938.

6 Helman, E. Personal communication to the author.

acid daily by mouth or hypodermically to all patients in the surgical service suspected of being deficient in vitamin C Wolfe and Hoebel⁷ in a recent article have recommended that unless the blood level can be followed patients with vitamin C deficiency should be given 1 Gm of ascorbic acid daily for nine to ten days and then given a maintenance dose of 300 to 500 mg daily until all wounds are healed These doses are considerably larger than have been thought necessary heretofore

Plasma Proteins—The relation between abnormally low levels of protein in the blood plasma and the presence of tissue edema has been known for a relatively long time, but only recently have the investigations of Ravdin and his associates⁸ (among others) shown the importance of this relation to surgical treatment These authors have shown that the edema which begins when the level of blood proteins falls below 7.5 Gm per hundred cubic centimeters involves the gastrointestinal tract as well as the subcutaneous tissues The gastric emptying time and the motility of the intestine are both decreased Ravdin has been able to show that in many instances obstruction at the site of anastomosis after operation is on the basis of a low level of plasma proteins Other investigations at the same clinic and elsewhere indicate that many wound disruptions and eviscerations may, in part at least, be dependent on poor healing of edematous tissues secondary to a deficiency of proteins in the plasma Thus, two important factors in the serious postoperative complication of wound dehiscence have recently been elucidated vitamin C deficiency and a low level of plasma proteins

Owing to restricted diet, anorexia, vomiting or faulty utilization of ingested protein, the patient with a gastrointestinal lesion frequently presents himself for operation with a definitely decreased concentration of plasma proteins In the case of such a patient the level of blood protein should be accurately determined by laboratory methods and the deficit corrected

So far no satisfactory clinical method for administration of proteins or their breakdown products directly to the blood stream has been developed Elman and Weiner⁹ have recently reported their ability to maintain patients in positive nitrogen balance by intravenous injection of hydrolyzed casein to which have been added small amounts of tryptophan and methionine At present, however, such a procedure cannot be considered practical for the general surgeon Similar investigations now being pursued by Ravdin also give hope for the future

⁷ Wolfe, I. A. and Hoebel, F. C. The Significance of Cerebric Acid Deficiency in Surgical Patients, Surg, Gynec & Obst 69 745 1939

⁸ Ravdin, I. S. Some Recent Advances in Surgical Therapeutics, Ann Surg 109 321, 1939 Thompson, Ravdin and Frank²

⁹ Elman, R. and Weiner, D. O. Intravenous Alimentation with Special Reference to Protein (Amino Acid) Metabolism J. A. M. A 112 796 (March 4) 1939

The transfusion of whole blood or of blood plasma will effectively and safely raise the level of blood proteins. Since many patients with a low level of plasma proteins also have secondary anemia, the giving of whole blood is often doubly indicated. Occasionally, however, after multiple transfusions have been given the hemoglobin content of the blood is found to be normal, while the protein content of the plasma is still below the desired level of 7.5 Gm per hundred cubic centimeters. In such instances, in the surgical service of the University Hospitals a practice has been made of centrifuging citrated whole blood and injecting intravenously the plasma thus obtained. At present all blood remaining in the blood bank for ten days is withdrawn and centrifuged. The plasma is decanted off and bottled for future use. The length of time for which this fluid may be preserved is dependent apparently only on maintenance of its sterility. Plasma may be obtained relatively easily with a minimum of equipment in this manner, and in my experience may be safely administered without regard to blood groups in amounts up to 500 cc at any one time. Certain hospitals are fortunate in having available lyophilized serum or plasma. The manufacture of this product requires such elaborate technic and expensive equipment, however, that its use must remain restricted until it is made commercially available.

In the postoperative period and particularly if convalescence is prolonged, maintenance of a normal level of blood protein is just as important as preoperative correction of any deficiency in this respect. Surgeons must realize that the protein stores within the body available for production of blood proteins are not inexhaustible and that determination of the level of blood protein will frequently give a clue to the proper treatment of unexpected and sometimes baffling complications.

Administration of Fluids—The proper administration of fluids to patients with disease requiring operation has probably been more thoroughly investigated than any other phase of preoperative and postoperative treatment. All surgeons should be familiar with the excellent contributions to this subject made by Coller and Maddock and their collaborators.¹⁰

Since in health some 6,000 to 8,000 cc of fluid is secreted each twenty-four hours into the upper part of the gastrointestinal tract and reabsorbed in the ileum and colon, the surgeon must appreciate the significance and harmful effects of those conditions which interfere with this continual process if his patients are to be treated properly. Failure

10 (a) Coller, F. A., Dick, V. S., and Maddock, W. G. Maintenance of Normal Water Exchange with Intravenous Fluids, *J. A. M. A.* **107**:1522 (Nov. 7) 1936. (b) Coller, F. A., Bartlett, R. M., Bingham, D. L. C., and Maddock, W. G. The Replacement of Sodium Chloride in Surgical Patients, *Ann. Surg.* **108**: 769, 1938.

to reabsorb these secretions produces in a relatively short time alkalosis and dehydration, which may finally result in the shocklike state of hypochloremia. Persistent vomiting, long-continued diarrhea and loss of secretions through fistulas, either external or internal (as in cases of gastrocolic fistula in which the absorptive portion of the gastrointestinal tract is "short circuited"), all produce a decrease in the level of blood chlorides and dehydration. It is well, therefore, when an intestinal lesion exists and there is reason to suspect even a slight degree of alkalosis or dehydration, to determine the level of blood chlorides before operation. If any deficiency is found, it should be corrected by paraoral administration of saline solution. If dehydration is still evident after this has been accomplished, more fluid, in the form of 5 or 10 per cent dextrose solution, should be given. Collier and his associates^{10b} have stated and shown by clinical trial that 0.5 Gm of sodium chloride per kilogram of body weight should be given for each 100 mg by which the level of blood chloride is found to be below the normal level of 560 mg per hundred cubic centimeters.

Some surgeons may find it inconvenient to determine the level of blood chlorides. An alternative method for regulating the administration of paraoral fluids is available. Chlorides are threshold substances and are excreted by the kidneys in appreciable amounts only after the body has retained all it requires for metabolic needs. Therefore, one can be reasonably certain that a patient who is fully hydrated and excretes 3 Gm or more of chlorides (expressed as sodium chloride) in his urine daily is in adequate sodium chloride balance. Quantitative determination of urinary chlorides can be made easily with a minimum of apparatus.¹¹ This is the method employed in the surgical service of the University Hospitals for the purpose of checking the chloride balance of patients from day to day when fluids are given by paraoral routes. Fantus¹² as well as Standard¹³ has found this method practical and satisfactory for clinical use. It seems preferable, however, to determine the initial level of blood chloride in order properly to evaluate the status of the patient when treatment is begun. As a working rule, my associates and I have found it feasible to give fairly routinely each day 1,500 cc of physiologic solution of sodium chloride in the morning and 1,500 cc of 5 or 10 per cent dextrose in distilled water in the afternoon or evening. These quantities are varied from time to time as the determination of the urinary excretion of chloride expressed as sodium chloride indicates.

¹¹ Paine, J. R., and Armstrong, W. G. A Study of the Fluid and Sodium Chloride Balance in Patients Treated with Continuous Suction Applied to Indwelling Duodenal Tubes, *Surg, Gynec & Obst* **68** 751, 1939.

¹² Fantus, B. Fluid Post-Operatively. Statistical Study, *J. A. M. A.* **107** 14 (Feb. 4) 1936.

¹³ Standard, S. Water and Salt Metabolism. Internat. Abstr. Surg. **67** 391 1938, in *Surg, Gynec & Obst*, October 1938.

Most surgeons now prefer subcutaneous or intravenous administration of fluids for patients who are unable to imbibe them. To avoid any danger of overloading the heart, with consequent pulmonary edema, a minimum rate of injection must be followed with patients to whom large amounts of fluids are given intravenously. Winslow¹⁴ has shown recently that although the major portion of the dextrose injected intravenously in 5 or 10 per cent solution is held by the body whatever the rate of the injection, for full utilization of the dextrose and for decreasing the diuretic effect of its injection to a minimum administration must be made at a relatively slow rate. These optional slow rates of injection, however, are often difficult to achieve in a busy surgical ward and often produce considerable discomfort for the patient by causing the arm to be immobilized in the extended position for several hours each day. For these reasons, at the University Hospitals an increasing proportion of fluids administered by the paracostal route, especially those administered to patients within the older groups, is being given by hypodermoclysis.

Proctoclysis has fallen from favor. Clinical observations have shown that the amount of fluid which can be absorbed in this way varies a great deal. In certain instances, however, the use of this method is indicated. My associates and I have confined our use of it to the unusual case in which loss of fluid and electrolytes by gastroduodenal aspiration is immoderate or prolonged. In such circumstances it has been felt that it is wise to have the patient reabsorb by proctoclysis as much of this aspirated fluid as possible. The thought in mind has been that such fluid may contain important substances other than sodium chloride which are difficult to restore by artificial means. In favorable cases 600 to 800 cc. of this fluid may be absorbed by the patient daily.

NEWER SURGICAL TECHNIQUES

For years the surgeon's hand has frequently been stayed by the fear of development of postoperative peritonitis. The major portion of the mortality following intestinal resections and the various types of anastomoses can be directly related to this complication. Various stage procedures, such as the Block-Mikulicz operation for colonic lesions, became standard because in large measures they decreased the danger of peritonitis.

The development of special instruments, such as the Rankin forceps and others built on the same principle, however, has somewhat changed the surgeon's attitude. Some clinics by the use of these newer methods have been able to show a great improvement in mortality rates. Especially

¹⁴ Winslow, S. B. Dextrose Utilization in Surgical Patients, *Surgery* 4: 867, 1938.

is this so in the surgical treatment of colonic lesions Stone¹⁵ (among others) has reported results from one stage resections of the colon that are better than those frequently obtained by the Bloch-Mikulicz technic

Increasing efforts are being made to develop these aseptic methods of anastomosis Wangenstein¹⁶ has recently described a method which by the use of modified Martzloff clamps gives consistently good results from all types of gastrointestinal procedures The future should see growth in the popularity of these newer methods and an improvement in the results obtained

PROPHYLAXIS AND TREATMENT OF POSTOPERATIVE PERITONITIS

Substances Producing Leukocytic Reactions in the Peritoneal Cavity

—As has been stated, peritonitis is by far the most frequent cause of death after surgical procedures performed on the small intestine and the colon Efforts to remedy this situation have not been lacking, however The vaccine developed by Baigin, although never accepted generally as being of great value, was used enthusiastically in some clinics Rankin,¹⁷ once an ardent advocate of this prophylactic measure, has recently withdrawn his approval of it Other methods and products, however, have been developed to take its place In general, these methods all attempt to produce increased leukocytosis within the peritoneal cavity Colibactrigen, developed by Steinberg,¹⁸ has received the approval of several nationally known surgeons and is probably the best known of these products I have had no personal experience with colibactrigen, but I cannot help being impressed by the favorable reports concerning its use which have appeared Rea¹⁹ has found experimentally in rabbits that a degree of protection against peritonitis is produced by intraperitoneal injection of sodium ricinoleate The use of amniotic fluid for the same purpose has been favorably reported on by Johnson²⁰

15 Stone, H, and McLanahan S Surgical Aspects of Carcinoma of the Large Bowel, J A M A **113** 2282 (Dec 23) 1939

16 Wangenstein, O H Aseptic Gastric Resection A Method of Aseptic Anastomosis Adaptable to Any Segment of the Alimentary Canal (Esophagus Stomach, Small or Large Intestine) Including Preliminary Description of Subtotal Excision of the Acid Secreting Area for Ulcer, Surg, Gynec & Obst **70** 59, 1940

17 Rankin, F W Resection of Recto-Sigmoid by Single or Graded Procedures, Ann Surg **104** 628, 1936

18 Steinberg, B Experimental Background and Clinical Application of Escherichia Coli and Gum Tragacanth Mixture (Coli-Bactrigen) in Prevention of Peritonitis, Am J Clin Path **6** 253, 1936

19 Rea, C E Personal communication to the author

20 Johnson H L Amniotic Fluid Concentrate as an Activator of Peritoneal Immunity Surg Gynec & Obst **62** 171 1935

Trusler²¹ and Warren²² Priestley and McCormack²³ have expressed the opinion that immunotransfusions of serum are valuable for patients with peritonitis from a ruptured appendix

Roentgen Irradiation—Pratt²⁴ has reported the beneficial effects of preoperative roentgen irradiation of the abdomen and pelvis in patients with carcinoma of the colon Peritonitis did not develop in any of a series of 51 patients thus treated Kelly and Dowell²⁵ have also advocated irradiation of the abdomen in certain patients with peritonitis Their attention has been particularly directed toward the treatment of peritonitis due to rupture of the inflamed appendix

Sulfanilamide—Peritonitis occurring after intestinal operations is usually a mixed infection, with various strains of streptococci and staphylococci and the colon bacillus forming the most important and toxic elements On the basis of present knowledge of the effects of sulfanilamide it might be rationally assumed that the effect of its administration would be uncertain and disappointing Recent investigations by three investigators, however, have indicated that its administration is worth while Ravdin, Rhoads and Lockwood²⁶ have stated that the mortality incident to peritonitis associated with appendicitis is definitely decreased by large doses of sulfanilamide Garlock and Seley²⁷ have reported the incidence of peritonitis after operations on the colon to be considerably decreased if sulfanilamide is given for three days before operation (with the blood level maintained at 5 to 6 mg per hundred cubic centimeters) and its administration continued into the immediate postoperative period Curreri²⁸ has found with dogs that if sulfanilamide is given the mortality attending perforation of the intestinal tract is appreciably decreased Although my own experience is meager, it

21 Trusler, H M Peritonitis An Experimental Study of Healing in the Peritoneum and the Therapeutic Effect of Amniotic Fluid Concentrate, Arch Surg **22** 983 (June) 1931

22 Warren, S The Effects of Amniotic Fluid on Serous Surfaces, Arch Path **6** 860 (Nov) 1928

23 Priestley, J T, and McCormack, C J Generalized Peritonitis Secondary to Rupture of Appendix, with Special Reference to Serum Therapy, Surg, Gynec & Obst **63** 675, 1936

24 Pratt, J R One Stage Operation for Resection of Recto-Sigmoid and Rectum for Carcinoma (With or Without Hysterectomy), Am J Obst & Gynec **36** 209, 1938

25 Kelly, J F, and Dowell, D A Roentgen Treatment of Acute Peritonitis and Infections with Mobile X-Ray Apparatus, Nebraska M J **24** 164, 1939

26 Ravdin, I S, Rhoads, J E, and Lockwood, I S The Use of Sulfanilamide in the Treatment of Peritonitis Associated with Appendicitis, Ann Surg **111** 53, 1940

27 Garlock, J H and Seley, G P The Use of Sulfanilamide in Surgery of the Colon and Rectum Preliminary Report, Surgery **5** 787, 1939

28 Curreri, A R Personal communication to the author

would seem, judging from the investigations mentioned as well as from a few cases personally observed, that sulfanilamide must be considered a worth while addition to the present inadequate means of treatment of peritonitis

GENERAL CONSIDERATIONS OF PREOPERATIVE TREATMENT

The somewhat trite expression that patients should be brought to the operating room in the best possible condition should not lose any of its importance through repetition. In no branch of surgery is it more important to weigh carefully all the circumstances in the case and think out each step of the treatment and of the operation beforehand than in surgical treatment of the gastrointestinal tract. It is realized that in certain exigencies uncontrollable circumstances may prevent the use of certain recommended and otherwise desirable procedures. The surgeon who accepts the responsibility for the care of the patient must be the judge of the methods to be employed and the effort to be expended in their application.

Conditions Requiring no Special Preoperative Treatment—Many patients with acute lesions of the intestinal tract, such as inflammations of the vermiform appendix and Meckel's diverticulum, require no special preoperative treatment. Such patients have usually been in good health prior to the acute attack and require only the routine preoperative preparation indicated for any major surgical procedure. If vomiting has been severe or prolonged, attention should be paid to proper hydration of the patient by means of saline solution administered intravenously or subcutaneously. Before any general anesthetic is given the surgeon should assure himself that the patient's stomach is empty. This is easily accomplished in the usual case by omitting all solid foods for six hours before operation and restricting ingestion of fluids during the immediate preoperative period. Should any doubt exist as to whether the stomach is empty at the time of operation, the question should be definitely settled by aspirating the stomach with a tube large enough to remove its contents.

In order to obviate the possibility of an involuntary defecation during the period of anesthesia and to insure an added degree of postoperative comfort, the lower part of the colon should be emptied by administration of a mildly irritating enema. In cases of acute appendicitis or in the presence of inflammatory lesions in the colon the preoperative enema should be omitted.

It is essential of course, that patients be brought to the operating room adequately sedated and that measures be taken to reduce the production of mucus in the mouth, the nasopharynx, the trachea and the bronchial tree during the period of anesthesia. The time-tried combination of $\frac{1}{6}$ grain (0.01 Gm.) of morphine sulfate and $\frac{1}{150}$ grain

(0.4 mg) of atropine sulfate given hypodermically thirty to forty-five minutes before the operation is begun is usually quite satisfactory. The sedation can be increased to advantage in selected cases by administration of 1 to $1\frac{1}{2}$ grains (0.06 to 0.09 Gm) of sodium pentobarbital forty-five minutes before the morphine and atropine are given. Pantopon (a mixture of hydrochlorides of opium alkaloids) as a substitute for morphine is preferred by many surgeons. Certain precautions should be heeded in administration of morphine to children and to elderly or weak adults. Children are sensitive to morphine and should be prepared for operation by the substitution of codeine sulfate in 1 grain (0.06 Gm) doses or smaller, depending on the age and size of the child. In old age also morphine is not a safe drug for routine use in the usual physiologic dosage for preoperative preparation. No one desires to begin an operation with the patient's respirations decreased to 8 or 10 a minute, a condition which will occasionally occur if $\frac{1}{4}$ or $\frac{1}{6}$ grain (0.015 or 0.01 Gm) doses of morphine sulfate are routinely used preoperatively for debilitated elderly patients.

The use of $\frac{1}{200}$ or $\frac{1}{100}$ grain (0.3 or 0.6 mg) of scopolamine hydrobromide U. S. P. in place of the usual $\frac{1}{150}$ grain (0.4 mg) or $\frac{1}{100}$ grain (0.6 mg) of atropine sulfate is fairly common. Since this drug has an inhibitory effect on the nasopharyngeal secretions and at the same time is a sedative, many prefer it. I have had no extensive experience with it.

Atropine sulfate is much better tolerated by adults than by infants and young children. When used, it should be given in sufficiently large doses to produce its physiologic effect. The average adult dose of $\frac{1}{150}$ or $\frac{1}{100}$ grain is usually well tolerated. Doses of the magnitude of $\frac{1}{600}$ grain (0.1 mg) or $\frac{1}{300}$ grain (0.2 mg), however, occasionally produce atropine reactions in the young, with flushing of the face, elevated temperature and rapid pulse. If such a reaction occurs, it is best, unless the operation is urgently indicated, to postpone all surgical treatment for a few hours or even until the next day in order that the reaction to the drug may subside.

Conditions in Which Preoperative Treatment May Be Indicated but in Which the Necessity of Operation Is Paramount—Certain conditions of the small intestine and of the colon necessitate operation as soon as the diagnosis is made despite obvious indications for various preoperative procedures. Such lesions include perforations, severe acute bleeding, strangulation obstruction and simple obstruction of the large bowel.

Despite the urgency for operation, no patient in shock or collapse should be subjected to a surgical procedure. Any patient with an intestinal lesion will be a much better surgical risk if time is taken before operation to combat adequately any shock which may be present with

large blood transfusions (or administration of physiologic solution of sodium chloride if the collapse is due to hypochloremia) In many instances the administration of blood or saline solution can be continued with benefit during the operation Other features of treatment, such as external application of heat and administration of morphine, may be of value, but the chief reliance should be placed in administration of whole blood combined with use of the Trendelenburg position If the shock is not too severe, merely placing the patient in the Trendelenburg position will frequently raise the systolic blood pressure 20 to 25 millimeters of mercury and maintain it above the critical level until an ample amount of blood can be given During the past ten years in the surgical service of the University Hospitals it has been the practice in an emergency to give any patient group 4 (O) blood without matching or cross matching No reactions have occurred which have caused my associates and me to regret this practice

Gastroduodenal aspiration should be instituted as soon as possible to empty the upper reaches of the gastrointestinal tract and prevent the development of distention This should be continued during and after operation

In cases of this kind preoperative medication can be given, but the preoperative enema is hardly indicated

Conditions Which Are Greatly Benefited by Intelligently Directed Preoperative Treatment—Patients with diseases in this class have usually had their lesions some time and suffer from the chronic effects of nutritional disturbances, combined with recurrent bleeding or partial obstruction Conditions responsible for these chronic effects include the various causes of partial obstruction, such as congenital malposition of the intestines, various tumors of the bowel (such as polyps and carcinomas), gastrocolic fistulas, nonmalignant strictures, regional enteritis and ulcerative colitis The initial effort of the surgeon in the presence of this type of condition should be the making of an accurate diagnosis Immediate operation is not indicated, and sufficient time should be taken to carry out a comprehensive plan of preoperative treatment Vitamin deficiencies should be corrected by administration of vitamins B and C Anemia should be corrected by repeated blood transfusions until the hemoglobin level has been raised to 75 or 80 per cent at the time of operation If the level of serum proteins remains low after a satisfactory hemoglobin value has been attained, additional amounts should be given as transfusions of plasma The use of gastro-duodenal aspiration to relieve the distention and symptoms associated with partial obstruction is frequently indicated Usually the simple technique described by Wangenstein²⁹ is sufficient but in selected cases

²⁹ Wangenstein, O H The Therapeutic Problem in Bowel Obstruction
S. Field III Charles C Thomas Publisher, 1937

the use of the Miller-Abbott tube by the method described by Abbott and Johnston³⁰ frequently is helpful. Certain obscure lesions of the small intestine can occasionally be accurately diagnosed by the use of this tube and roentgen examination that might otherwise be missed. The fluid balance of the patient should be determined accurately and corrected as has been described. The operative procedure itself is, within certain limits, an elective procedure and should be undertaken only when the surgeon is convinced that the general condition of the patient cannot be further improved.

Other features of preoperative treatment previously discussed, such as preoperative medication, enemas and omission of food for some hours before operation, apply with equal force to this class of patient.

GENERAL CONSIDERATIONS OF POSTOPERATIVE TREATMENT

The chief aims of postoperative treatment should be to secure adequate rest and comfort for the patient over a sufficient period to insure that healing takes place at the site of operation and to prevent as far as possible pulmonary complications and venous thrombosis.

Decompression—Gastroduodenal Aspiration. Probably the most important element in the postoperative treatment of patients subjected to operations on the small intestine and the colon is continuous gastro-duodenal aspiration. In my opinion this procedure secures the greatest degree of rest, both physical and physiologic, for the gastrointestinal tract that can be obtained.

So-called paralytic (adynamic) ileus occurs to some extent after any operation of magnitude within the abdomen. After operations during which the bowel and its mesentery must of necessity be more or less manipulated and traumatized, the more severe degrees of this condition occur. The stomach and intestine become distended with gas, derived principally from swallowed air but appreciably augmented by fermentative processes and by diffusion from the blood. Another important factor contributing to this distention is the relatively large quantity of fluid poured into the upper reaches of the gastrointestinal tract by the digestive glands.

This distention is best prevented or controlled by means of constant mild suction applied to an indwelling duodenal tube. The details and technic of this procedure have been fully described elsewhere. Many variations of the original apparatus described by Wangensteen and Paine³¹ have appeared, but any apparatus which maintains a constant

30 Abbott, W. O., and Johnston, C. G. Intubation Studies of the Human Small Intestine, Surg., Gynec. & Obst. 66:691, 1938.

31 Wangensteen, O. H., and Paine, J. R. Nasal Catheter Suction Siphonage Its Uses and the Technic of Its Employment, Minnesota Med. 16:96, 1933.

negative pressure of 70 to 100 cc of water and which allows the quantity of aspirated fluid to be measured should be satisfactory

Two purposes are served by aspiration. The first is the removal as far as possible of the gaseous and fluid contents of a digestive tract which is unable to transport and dispose of them in a normal manner. The second is the prevention as far as possible of any further accumulation of gas and fluid in an already distended digestive tract.

It has been adequately shown by McIver and his associates³² as well as by Hibbard³³ that 70 to 80 per cent of the gases found in the intestinal tract are derived from swallowed air. Any method, therefore, such as gastroduodenal aspiration, which removes swallowed air as rapidly as it gains entrance to the stomach will effectively prevent to a great extent any distention that may already be present from becoming greater. If, therefore, aspiration is begun before distention appears it is usually satisfactory to permit the distal end of the duodenal tube to remain in the stomach. In such cases, although the duodenum is frequently intubated incidentally, no serious effort is made to intubate it.

If the tip of the suction tube remains in the stomach the effect of aspiration on the contents of an already distended small bowel is somewhat doubtful. Considerable quantities of fluid and gas may be removed from the lower reaches of the intestine if the pylorus is relaxed or if regurgitation into the stomach occurs regularly. This cannot be depended on, however. In any case, therefore, in which considerable distention is already present a consistent effort should be made to cause the tip of the tube to pass beyond the pyloric sphincter.

Incidental to the main purpose of continuous aspiration by the duodenal tube but important in their own right are additional advantages which accrue from this procedure. Suture lines in the intestinal walls are protected from possible disruption by an increased intraluminal pressure, and the incidence of obstruction from adhesions in the immediate postoperative period is greatly decreased.

It is our practice to begin suction on each patient subjected to major intestinal operations except simple appendectomy before the patient goes to the operating room, since experience has shown that by this means postoperative nausea, vomiting and distention can consistently be prevented. Suction is thus maintained during operation and for several days thereafter. Patients are allowed to take by mouth up to 2000 cc of clear fluids daily during this period. At least once each twenty-four

³² McIver, M. A., Benedict, E. B., and Cline, J. W. Post-Operative Gaseous Distention of the Intestine. Experimental and Clinical Study, *Arch. Surg.* **13** (Oct.) 1926.

³³ Hibbard, J. S. Gaseous Distention Associated with Mechanical Obstruction of the Intestine, *Arch. Surg.* **33** 146 (July) 1936.

hours the quantities of fluid and gas aspirated are noted. Particular attention is paid to the quantity of aspirated fluid, for this must be returned to the patient or compensated for by administration of saline solution as described in the section on fluid administration.

The exact time at which suction should be discontinued depends in general on the degree and duration of the ileus as well as on other considerations which may be present in the individual case. The average patient requires suction for four to six days after operation. Before finally removing the suction tube it is always well to test the patient's ability to be comfortable without it by clamping the tube for a time, during which the patient is allowed to take a moderate amount of oral fluid. If the patient can tolerate the suction tubes clamped for six to eight hours and imbibe during this time three to four glasses of water or other fluid without the appearance of distention, nausea or vomiting, the duodenal tube may be removed without fear that it may have to be reinserted and suction renewed after a short time.

Especially, in certain instances in which an obstruction exists which the surgeon has reason to believe will be temporary it may be desirable to maintain suction for a relatively long time. Under these circumstances maintenance of the nutrition of the patient becomes a serious matter. It has been found satisfactory in these cases to clamp the suction tube for intervals of one to two hours several times a day. During these intervals nourishing liquids are given by mouth or injected through the tube. Some portion of this fluid will be retained by the patient.

The development of the Miller-Abbott double lumen tube has increased the possibilities of postoperative treatment of patients with intestinal lesions. Decompression of the entire gastrointestinal tract down as far as the cecum can be carried out more quickly and efficiently than is possible with the method of Wangensteen²⁹. The use of this type of tube, however, will probably remain limited to the unusual case in which the simpler apparatus and technic of Wangensteen prove satisfactory. Experience has shown that decompression of a greatly distended small bowel in the presence of peritonitis when peristaltic movements are minimal is sometimes far from satisfactory when the simple duodenal tube is used. In such cases, perhaps, it is best to use the Miller-Abbott tube, for it is reported that if this tube can be made to pass the pylorus and its balloon inflated the intestine can be "negotiated" fairly effectively³⁴. As has been emphasized, however, this situation should rarely occur if patients are properly treated postoperatively and suction is begun before distention becomes great.

34 Johnston, C. G., Penberthy, G. C., Noer, R. J., and Kenning, J. C. Decompression of the Small Intestine in the Treatment of Intestinal Obstruction, *J. A. M. A.* **111** 1365 (Oct. 8) 1938.

High Oxygen Concentrations in Respired Air—Surgeons have now at their command an additional method to combat the gaseous distention associated with paralytic ileus. Fine and his co-workers have pointed out and proved by clinical trial the decompressing effect of breathing high concentrations of oxygen for relatively long periods. Since 55 to 60 per cent of the intestinal gases are nitrogen, it is possible to remove this as well as other portions of the gases by diffusion if the patient is made to breathe an atmosphere in which the partial pressure of these gases is maintained at a lower level. This can be accomplished if the patient is supplied with an oxygen concentration of over 85 per cent for his respiratory needs. I have used this method successfully on numerous occasions. It is particularly valuable when used in conjunction with gastroduodenal aspiration in the treatment of paralytic ileus when well developed distention must be combated.

The chief difficulty of the method arises in the technical details of its application. The generally used oxygen tent is not satisfactory, because oxygen concentrations of over 60 per cent cannot be economically maintained. Fine has used a modified tent with success. In my experience the Lovelace-Boothby mask is admirably suited for the purpose. High oxygen concentrations can be maintained with a relatively small expenditure of oxygen, and aspiration by means of a duodenal tube can be carried on simultaneously. One objection can be raised, however, to this method of supplying oxygen. Not infrequently patients complain of the discomfort produced by the pressure of the mask on the face when it is worn for several days at a time.

It would seem best to consider the breathing of high oxygen concentrations only as an adjunct to gastroduodenal aspiration in the treatment of distention. While it may adequately remove gas from or prevent its accumulation in the gastro-intestinal tract, it does nothing specifically to the other important factor of distention, namely, fluid. Experience has shown that postoperative nausea and vomiting disappear only when the stomach is kept empty of both fluid and gas.

Drugs—Drugs, such as prostigmine, physostigmine, acetyl-beta-methylcholine hydrochloride (mecholyl), solution of posterior pituitary and pitressin, have frequently been recommended for use in the postoperative period because of their effect on the motor functions of the bowel. It has been claimed that they hasten the return of normal peristalsis and the expulsion of feces and gas, at the same time decreasing the discomfort of gas pains. Such drugs should find little place in the postoperative phase of surgical therapy of the intestine if appropriate

35 Fine, J., Banks, B. M., Sears, J. B., and Hermanson, L. The Treatment of Gaseous Distention of the Intestine by Inhalation of Ninety-Five Per Cent Oxygen, *Ann Surg* 103 375, 1936.

measures are taken to insure against the development of distention Gastroduodenal aspiration will control distention of the small bowel more effectively than any drug Troublesome accumulations of gas in the lower part of the colon may be relieved by insertion of a rectal tube for a short period several times a day

Use of Narcotics—After operation some narcotic drug, such as morphine, pantopon (a mixture of hydrochlorides of opium alkaloids), dilaudid hydrochloride or codeine, must be used in effective doses frequently enough to relieve in large measure the pain and discomfort which inevitably follow any abdominal surgical procedure Morphine sulfate, $\frac{1}{2}$ grain (0.01 Gm.), given every four hours as needed, is usually employed for this purpose at the University Hospitals for the average adult patient Within forty-eight hours after operation most of the acute pain will have subsided, and the amount given can be rapidly decreased or the drug omitted

Every surgeon should be thoroughly acquainted with the various analgesic drugs available and should use them to fit the circumstances of each case in which their administration is indicated Some patients react untowardly to many of these drugs with urticaria, itching, nausea or vomiting In such instances the knowledge and skill of the surgeon may be taxed to the utmost to achieve the desired result, which is comfort for his patient

Tracheal Aspiration—Periodic aspiration of the trachea and the larger bronchi during the immediate postoperative period, as suggested by Haight,³⁶ is a procedure of major significance in surgical treatment A urethral catheter attached to a suction machine, or, lacking this, a large syringe, is passed through the nose into the trachea, and any mucus which may have collected there is aspirated This is of great value for the prophylaxis of atelectasis and pneumonia Not every patient will require aspiration, but for those who have abundant mucus this procedure, carried out three or four times a day, removes surprisingly large amounts of bronchial secretions Thus, the necessity for the patient's coughing and the disrupting strains on the abdominal wound are largely eliminated

At the completion of every operation the pharynx and trachea should be thoroughly aspirated by the anesthetist In those instances in which production of mucus has been excessive during the operation and especially after prolonged procedures in the upper part of the abdomen, it is best to do this under direct vision through a bronchoscope before the patient leaves the operating table

³⁶ Haight, C Intratracheal Suction in the Management of Postoperative Pulmonary Complications *Ann Surg* 107 218 1938

Use of Trendelenburg Position—After a prolonged operation with deep anesthesia, much is to be gained by keeping the patient after his return to bed in a "steep Trendelenburg" position for twelve to twenty-four hours or at least until he has fully recovered from the anesthesia and from any postoperative shock which may occur. This position insures good drainage of the bronchial secretions during the time when the cough reflex is diminished and guards against atelectasis.

The favorable effect of the Trendelenburg position on the low blood pressure of a patient in shock has been mentioned.

Treatment of Shock—Surgical shock after prolonged and difficult operations on the small intestine or the colon occurs not infrequently. After returning to his bed, any patient whose systolic blood pressure remains at 90 mm of mercury or lower after he has been placed in the Trendelenburg position should be considered to be in shock. Only one satisfactory treatment for this condition exists, and that is adequate blood transfusion. An adequate transfusion means administration of a sufficient quantity of blood to maintain the systolic blood pressure at a satisfactory level, whether this is 500 or 1,500 cc.

Active Movements by the Patient—After the patient's bed has been returned to the horizontal position, he should be turned from side to side every hour until the pain of the incision has subsided sufficiently to permit active movement on the part of the patient himself. From the beginning of the postoperative period patients should be encouraged to move their arms and legs actively and frequently. Such movements with their attendant increase in the flow of blood in the veins are the best protection obtainable against the development of thrombophlebitis. Coughing should be encouraged if mucus in the nasopharynx is at all troublesome, but only when the abdomen and the lower ribs on each side are held in by the hands of a nurse or attendant, so that too great a strain is not placed on the sutures of the abdominal wound.

Use of Oxygen for Elderly Patients—Surgical procedures performed on elderly patients seem to be better tolerated if the patient is kept in an oxygen tent with an atmosphere containing 50 to 60 per cent oxygen. Such treatment insures an increased amount of oxygen available to a probably weakened myocardium and to a brain which is possibly the seat of arteriosclerosis during a period in which the blood pressure tends to be below normal.

Administration of Fluids—Since patients who have undergone surgical procedures involving the intestinal tract must be "carried" for a relatively long time (four to six days) before returning to an adequate oral diet, proper administration of paraoral fluids becomes a major part of the postoperative treatment. Removal of large quantities of gastroduodenal secretions by suction through a duodenal tube or loss of fluids through fistulas occasionally complicates the situation further.

The surgeon is presented with two problems (1) supply of a sufficient amount of water to the patient to maintain an adequate output of urine and (2) administration of a sufficient amount of sodium chloride to replace that lost from the body in perspiration and in abnormal losses of fluid. In addition, a very small amount of sodium chloride is required to supply the normal metabolic demands of the body. Administration of excessive amounts of saline solutions, however, must be guarded against in order to prevent edema.

The proper technic for the administration of fluids has been briefly discussed elsewhere in the paper.

Diet and Enemas—In most instances patients may be allowed food by mouth as soon as gastroduodenal aspiration is discontinued. It is a wise plan to restrict the diet to liquids for the first twenty-four hours after removal of the duodenal tube, however, to be sure that the gastrointestinal tract will tolerate food. If this is so the diet can be increased rapidly. No bowel movement is necessary or should be expected until two or three days after the patient has resumed a fairly general diet. Enemas may be given as indicated, but if 1 ounce (30 cc) of liquid petrolatum is given once or twice a day as soon as the patient begins to eat the occasions for their use will be largely eliminated.

SPECIAL POINTS TO BE OBSERVED IN THE TREATMENT OF PATIENTS WITH INFLAMMATORY LESIONS

Appendicitis—Certainly any inflamed, unruptured appendix should be removed as an emergency procedure. After rupture has occurred, however, and peritonitis has developed, the surgeon must pause and weigh the benefits to be obtained by operation against the harmful effects which his interference may produce. The policy followed in the surgical service at the University Hospitals is firmly fixed. When the surgeon is convinced that the appendix is ruptured a conservative regimen is followed. Gastroduodenal aspiration is instituted, and paraoral fluids given intravenously or subcutaneously. Sulfamidamide is given in relatively large doses, 90 grains (5.8 Gm) a day. If an abscess forms it is observed for a time and drained if necessary. Appendectomy in such cases is carried out later, after the acute phase of the infection has subsided. The results of this form of treatment, used over a six year period, have been satisfactory.

Inflammation of Meckel's Diverticulum—The same general plan of treatment used for patients with appendicitis is employed in instances of inflammations of Meckel's diverticulum.

Regional Ileitis—If a definite diagnosis of regional ileitis is made an unusual amount of care should be exercised in choosing the method of treatment. The patient not infrequently has moderate anemia and suffers

from nutritional disturbances. A period of preoperative treatment will improve the general condition. No operation should be attempted during an acute phase of the disease. During a period of quiescence the abdomen may be explored and a short-circuiting anastomosis performed. Some weeks later the involved portion of bowel should be excised. The danger of peritonitis is always present, and proper prophylactic measures are indicated. Continuous gastroduodenal aspiration should be an essential part of the postoperative treatment.

Ulcerative Colitis—The most important point in surgical treatment of this condition is the decision as to the time to operate. Patients should be treated conservatively with a medical regimen until a regression has occurred and the general condition has improved. After adequate transfusions and restoration of the normal fluid balance and level of plasma protein a complete deviation of the fecal stream should be obtained by ileostomy. Peritonitis is an ever present danger in this condition and should be carefully guarded against. The usual methods of postoperative treatment, including blood transfusions for shock, gastroduodenal aspiration and administration of paraoral fluids, should be employed.

Diverticulitis of the Colon—This condition may not require operation. In the acute phase, if continuous gastroduodenal aspiration is instituted and sulfanilamide given, the infection in many cases will subside and the patient will do well if low residue diets supplemented with liquid petrolatum are given. When these measures prove ineffective the fecal stream should be completely deviated by a colostomy proximal to the site of inflammation. If gastroduodenal aspiration is continued after operation, one need be in no particular hurry to open the colostomy wound. This can be done after three or four days, when danger of peritonitis at the operative site has passed. Any accumulation of gas in the colon which appears during this period can be aspirated through the unopened bowel at the site of colostomy with a needle and a syringe.

SPECIAL POINTS TO BE OBSERVED IN THE TREATMENT OF PATIENTS WITH OBSTRUCTIVE LESIONS

Continuous gastroduodenal aspiration is indispensable in the treatment of all patients with intestinal obstruction. It is important to realize, however, that this method alone, without an accompanying surgical operation, should never be used in cases of strangulation obstruction or acute simple obstruction of the large bowel. These types of ileus always demand immediate surgical intervention as soon as any shock which is present can be treated with blood transfusions. Aspiration of the stomach and duodenum will never relieve the obstruction to venous return in cases of strangulation nor can it be depended on to decrease distention.

due to an obstructed colon. In most instances the ileocecal valve prevents retrograde passage of gas and fecal material from the large intestine.

Partial or complete simple mechanical obstruction can be controlled adequately and relents frequently (unless due to a lesion intrinsic in the intestinal wall, such as a stricture or a tumor) after thirty-six to forty-eight hours of aspiration. Patients with obstruction in whom decompression by aspiration cannot be accomplished within forty-eight hours or in whom distention recurs after decompression should be operated on. Much will have been gained however by this preoperative period of aspiration. The risk associated with the necessary operation will be much less if this period is intelligently used to prepare the patient adequately in ways indicated elsewhere in this communication. Particular attention should be paid to the correction of dehydration, alkalosis and hypochloremia.

In order to insure as effectual a decompression as possible in any case of intestinal obstruction, care should be taken to pass the tip of the duodenal tube beyond the pyloric sphincter. Many cases come to mind in which decompression was dishearteningly slow until the duodenum was intubated. In other cases conservative decompression had to be given up and operation performed owing to inability to pass the tube beyond the stomach. In certain of these difficult cases the use of the Miller-Abbott tube is indicated.³⁴

In the presence of obstruction the choice of operation is important. When strangulation is present the infarcted segment must, of course be either exteriorized or resected. When possible exteriorization is perhaps the better choice, but in certain instances in which the obstruction is high, resection and anastomosis are imperative. In cases of simple obstruction, if decompression cannot be accomplished preoperatively no attempt should initially be made to remove the obstruction *per se*. Rather, a decompressive type of operation, such as an enterostomy or a colostomy, should be performed first, and the obstruction, if it still persists, removed at a second operation. Experience has shown that postoperative peritonitis occurring in the presence of obstruction is almost invariably fatal, so that any operation performed must be aseptic.

NEOPLASMS

Tumors of the small intestine and of the colon should usually be resected if possible. The treatment of these lesions, inasmuch as they frequently produce obstruction, has been already touched on in the preceding paragraphs. Anemia from recurrent bleeding must frequently be treated before removal is considered. Primary resection with anastomosis has always been the operation of choice for nonobstructing tumors of the small bowel and remains so today. The attitude of surgeons concerning similar lesions in the colon, however, is changing. Because

of the increased danger of postoperative peritonitis and because colostomy was found to be so much better tolerated than ileostomy or jejunostomy, stage procedures, such as the Bloch-Mikulicz operation, long enjoyed the well justified approval of most surgeons. The newer developments, of relatively aseptic methods of resection and effective means to decrease the incidence of postoperative peritonitis, have recently brought about an increasing tendency to employ the method of primary resection.

By far the most important phase of the postoperative treatment of these lesions is the use of continuous gastroduodenal aspiration for a sufficient period (five to six days) to insure adequate healing of the anastomotic suture lines.

SUMMARY

Surgical lesions of the small intestine and of the colon may be classified under three heads: (1) inflammatory lesions, (2) obstructive lesions and (3) neoplasms not producing obstruction. Recent developments have improved with the preoperative and postoperative treatment of the patient. These developments include (1) realization of the importance of vitamin B and vitamin C deficiencies, (2) knowledge concerning the deleterious effects of a low level of plasma proteins, (3) administration of fluids on the basis of physiologic requirements, (4) new surgical technics and (5) use of effective measures for prophylaxis and treatment of peritonitis.

The preoperative treatment of various types of lesions is briefly discussed. Certain general considerations of postoperative treatment are discussed. These include (1) decompression by (a) gastroduodenal aspiration, (b) high oxygen concentration in respired air and (c) use of drugs, (2) use of narcotics, (3) tracheal aspiration, (4) use of the Trendelenburg position, (5) treatment of postoperative shock, (6) active movements by the patient, (7) use of oxygen for elderly patients, (8) administration of fluids, and (9) diet and enemas.

Special points observed in the treatment of patients with inflammatory lesions, with obstructive lesions and with neoplasms are discussed.

EFFECT OF DIET ON COMPOSITION OF THE LIVER IN THE PRESENCE OF OBSTRUCTION OF THE COMMON BILE DUCT

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Careful preparation of the patient who is a poor surgical risk has greatly reduced the morbidity and mortality following surgical operations. In no field of surgery has this been more definitely proved than in the treatment of obstruction of the common bile duct and of serious hepatic injury. The histologic picture of the liver in these conditions often is one of extensive hepatitis, fibrous tissue replacement, parenchymal degeneration and fatty infiltration. Prior to operation, tests of hepatic function may give little or no indication of the degree of injury to the liver parenchyma. However, subsequent to the trauma of operation and anesthesia, hepatic insufficiency of such degree as to jeopardize the life of the patient may become evident. Extensive damage to the liver may be present before it is detectable by the tests now available. For this reason it is safe to assume that damage to the liver is present in all patients seriously ill with disease of the biliary tract, and every effort should be made to prepare the patient in a manner which will minimize the chances of hepatic incompetence subsequent to operation.

Since the work of Opie and Alford,¹ Schreiber,² and Davis, Hall and Whipple,³ a high carbohydrate diet or dextrose administered intravenously has been used in the preoperative preparation of jaundiced

Aided by the Merck Fund for Surgical Research

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1 Opie E L, and Alford, L B. The Influence of Diet on Hepatic Necrosis and Toxicity of Chloroform, *J A M A* **62** 895 (March 21) 1914, Diet and the Hepatic Lesions of Chloroform, Phosphorus, or Alcohol, *J Exper Med* **21** 1, 1915, Diet and Nephritis Caused by Potassium Chromate, Uranium Nitrate, or Chloroform, *ibid* **21** 12, 1915

2 Schreiber E. Ueber Stillung innerer Blutungen durch intravenöse Traubenzuckerinjektionen, *Therap d Gegenw* **54** 195, 1913

3 Davis, N C, Hall, C C, and Whipple, G H. Rapid Construction of Liver Cell Protein on Strict Carbohydrate Diet Contrasted with Fasting, *Arch Int Med* **23** 689 (June) 1919

patients Crile and Higgins,⁴ Walters,⁵ Ravdin⁶ and many others have reported on the beneficial effects which follow this type of therapy. As the result of much of this work it has been generally accepted that the presence of large amounts of glycogen in the liver in some manner offers protection to this viscus against a variety of hepatotoxic agents.

Evidence which Goldschmidt, Vars and Ravdin⁷ have recently published leads one to question the complete validity of the concept that the mere presence of glycogen in the liver acts to protect the organ against injury by volatile anesthetics. While these authors have not suggested that the carbohydrate which is fed part of which is deposited in the liver as glycogen, is of no value to the subject, they have implied that the glycogen in the liver, in so far as it indicates a previous adequate carbohydrate intake, exerts its influence by its effect on the metabolism of other foodstuffs in the body. These authors found that rats which had been on a low protein diet and in which the lipid content of the liver was high were maximally susceptible to injury by chloroform, while rats fed an adequate amount of protein in the diet, with livers low in lipid content, were maximally protected against injury. These investigations have recently been confirmed in experiments on the dog by Miller and Whipple.⁸

The presence of a large amount of fat in the liver would, as Wells⁹ suggested, result in retention of a large amount of the lipid-soluble hepatotoxic agent in the liver, and a longer time would be required for desaturation. Goldschmidt, Vars and Ravdin^{7a} found that a high protein diet ingested for some days prior to anesthetization to a degree protected the liver from necrosis even though the glycogen concentration of the liver was low and the fat concentration high. An adequate diet prior to anesthesia and operation for patients with disease of the biliary tract,

⁴ Crile, G. W., and Higgins, C. C. Prevention and Treatment of Post-operative Complications in Abdominal Surgery, *J. A. M. A.* **89** 1738 (Nov. 19) 1927.

⁵ Walters, W. Physiologic Considerations in the Treatment of Obstructive Jaundice, *J. A. M. A.* **87** 2153 (Dec. 25) 1926.

⁶ Ravdin, I. S. Some Aspects of Carbohydrate Metabolism in Hepatic Disease, *J. A. M. A.* **93** 1193 (Oct. 19) 1929.

⁷ Goldschmidt, S., Vars, H. M., and Ravdin, I. S. (a) The Influence of the Foodstuffs upon the Susceptibility of the Liver to Injury by Chloroform, and the Probable Mechanism of Their Action, *J. Clin. Investigation* **18** 277, 1939, (b) The Non-Specificity of Suspensions of Sodium Xanthine in Protecting the Liver Against Injury by Chloroform and the Probable Cause of Its Action, *ibid.* **18** 633, 1939.

⁸ Miller, L. L., and Whipple, G. H. Chloroform Liver Injury Increases as Protein Stores Decrease, *Am. J. M. Sc.* **199** 204, 1940.

⁹ Wells, H. G. Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, pp. 20 and 481, Delayed Chloroform Poisoning and Allied Conditions. A Note on the Cause of the Anatomic and Clinical Changes Observed, *J. A. M. A.* **46** 341 (Feb. 3) 1906.

therefore, becomes a matter of considerable importance. That a diet high in carbohydrate offers protection against the necrosis resulting from chloroform anesthesia while a diet high in fat increases the susceptibility of the liver to chloroform has been repeatedly confirmed since the original studies of Opie and Alford.¹

Diets high in protein have been considered inferior to¹⁰ or at best equal to¹¹ a carbohydrate diet in protective value. Starvation increases the susceptibility of the hepatic cells to injury by chloroform equal to¹⁰ or exceeding¹¹ that caused by a previous high fat diet.

The beneficial effect of a high carbohydrate diet in preventing injury to the liver following the use of chloroform can best be explained, in the opinion of Goldschmidt, Vars and Ravdin,^{7a} by the fact that when such a diet is administered, fat, if it is present in the liver in abnormal amounts, is displaced during the deposition of glycogen. The processes involved in this displacement need not be discussed here. This physiologic phenomenon was first pointed out by Rosenfeld.¹² He reported that in a number of physiologic and pathologic conditions in which the concentration of glycogen in the liver fell there occurred a fatty infiltration of the liver. The studies of Goldschmidt, Vars and Ravdin, however, demonstrate clearly that the liver may simultaneously contain a high concentration of glycogen and a high concentration of lipid. Under these conditions the glycogen per se, regardless of its concentration, does not protect the liver from injury. Channon and Wilkinson¹³ have demonstrated that a high protein diet is also beneficial in displacing hepatic fat. They found such a diet to be just as efficacious in reducing the hepatic lipid concentration as was the administration of choline, which Best and his co-workers¹⁴ had suggested as a physiologic accessory food factor which regulates the amount of fat in the liver.

Several years ago, when we were preparing our patients with hepatic disease with intravenously injected dextrose, we took biopsy specimens of the liver from patients with obstruction of the common bile duct. Approximately one third of the patients so prepared had amounts of

10 Davis, N. C., and Whipple, G. H. The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anaesthesia, *Arch. Int. Med.* **23** 612 (May) 1919.

11 Moise, T. S., and Smith, A. H. The Regeneration of Liver Tissue on Various Adequate Diets, *J. Exper. Med.* **40** 13, 1924. Smith, A. H., and Moise, T. S. The Regeneration of Liver Tissue During Nutrition on Inadequate Diets and Fasting, *ibid.* **40** 209, 1924.

12 Rosenfeld, G. Zur Lehre von der Fettwanderung, *Allg. med. Centr.-Ztg.* **83** 1051, 1900, Fettbildung, *Ergebn. d. Physiol.* **2** 50, 1903, Der Process der Verfettung, *Berl. klin. Wchnschr.* **41** 587, 1904, Fett und Kohlenhydrate, *ibid.* **43** 978, 1906, Eiweisskörper und Leberverfettung, *ibid.* **47** 1268, 1910.

13 Channon, H. J., and Wilkinson, H. Protein and the Dietary Production of Fatty Livers, *Biochem. J.* **29** 350, 1935.

14 Best, C. H., Huntsman, M. E., and Ridout, J. H. The "Lipotropic" Effect of Protein, *Nature, London* **135** 821, 1935.

fat in the liver which, had a volatile anesthetic been used during the operation would have conduced to some degree of degeneration or necrosis of the liver. Furthermore, the amount of glycogen in the liver when such a program was used during the preoperative period was never striking.

In view of the observations of Goldschmidt, Vars and Ravdin,^{7a} it seemed highly desirable to determine the diet best suited to prepare the "bad risk" for operation in cases of disease of the liver.

EXPERIMENTS

Healthy mongrel dogs, the majority of which were young and full grown, were selected for these experiments. Obstruction of the common duct was produced by ligation of the cystic duct or by cholecystectomy and double ligation and section of the common duct. When special diets were being fed, the food was carefully mixed and reenforced with the necessary vitamins and salts. The amount of food consumed each day by each dog was recorded. Biopsy specimens were taken from the liver before and after the periods of special feeding, so that the effect of the diet on the composition of the liver could be observed. The methods of analysis used in this work were the same as those previously reported.⁷ In this paper the term total fatty acids is used as an indication of the total lipid concentration of the liver.

Effect of Obstruction of the Common Duct—Twenty-one dogs which had been on the routine mixed diet of the animal house were subjected to total obstruction of the common duct. With this diet the concentration of fatty acids in the liver varied from 8 to 11 per cent by dry weight. Administration of the routine diet was continued after operation. The dogs were killed in from thirteen to thirty-five days after operation. The hepatic concentrations of fatty acids are given in table 1. It will be noticed that in 9 instances, or in more than one third, the concentration was such that had a volatile anesthetic been used some degree of injury to the liver would have resulted. In the remainder the concentration was within normal limits.

Inasmuch as an increased hepatic concentration of fatty acids was found in the dog subsequent to obstruction of the common duct in much the same incidence as in man, the dog was considered an appropriate animal to use in these investigations.

Effect of Diet or Diet and Choline Chloride on the Concentration of Fat in the Liver in the Presence of Obstruction of the Common Duct—Since a high concentration of fat in the liver did not occur in all of the dogs with obstruction of the common duct on the routine diet, dogs were placed on a high fat diet for two weeks prior to operation in order to increase the incidence of fatty livers. The dogs were then operated on, an initial biopsy specimen being taken from the liver and the common and cystic ducts being occluded. The majority of the livers contained an abnormally high concentration of fatty acids at the time of this operation. Various diets were then fed to determine the effect of these on the hepatic concentration of fatty acids in the presence of obstruction of the common duct.

The dogs usually gained weight during the two preoperative weeks on the high fat diet. After operation some difficulty was encountered at times in getting the dogs to eat certain of the diets, so that occasionally forced feeding and intravenous injections of dextrose were necessary. The dogs often lost some weight but as a rule did not fall much below their weight at the beginning of the

experiment The final weights are not especially significant, because of the presence of ascites in some animals

A summary of the results obtained by the various diets is given in table 2

a High Carbohydrate Diet About 80 per cent of the total calories which the dogs received were in the form of carbohydrate, a part of which was given intra-

TABLE 1—*Effect of Obstruction of the Common Duct on the Fatty Acid Concentration of the Liver*

Dog	Period of Obstruction, Days	Hepatic Fatty Acids, Gm/100 Gm	Comment
149	28	8.1	12 of 21 dogs (57 per cent) had normal concentrations of fatty acids in the liver
187	16	11.3	
200	14	9.7	
252	13	10.4	
203	27	10.7	
208	20	10.8	
205	30	8.8	
287	13	10.3	
316	30	9.4	
317	16	10.5	
366	20	9.3	9 of 21 dogs (43 per cent) had increased concentrations of fatty acids in the liver
370	20	8.1	
Average	20.6	9.8	
76	28	26.6	
79	18	31.1	
224	22	19.4	
227	15	25.1	
231	21	18.3	
260	37	14.3	
312	21	24.2	
313	21	20.2	
314	14	18.4	
Average	21.7	21.9	

TABLE 2—*Summary of Results*

Diet	No of Dogs	Weight, Kg			Days on Diet	Calories			Cal / Day	Hepatic Glycogen, Gm /100 Gm		Hepatic Fatty Acids, Gm /100 Gm		
		Initial	At			Protein, %	Fat, %	Carbohydrate, %		At Operation	Terminal Level	At Operation	Terminal Level	Change
			Operation	Terminal										
High protein and high carbohydrate	7	7.2	8.9	8.8	7	28	0	72	90	2.1	8.9	29.2	14.1	—54
High carbohydrate	4	7.2	7.5	6.4	14	8	12	80	88	2.2	3.4	30.9	15.5	—48
High carbohydrate with choline chloride	4*	6.6	7.5	7.1	8	7	11	82	71	1.3	2.3	30.1	18.9	—36
	7†	7.1	7.8	7.2	7	6	8	86	42	2.8	3.0	18.4	13.0	—29
Mixed diet	7	7.7	8.6	8.3	7	29	23	46	62	2.2	2.4	27.6	17.2	—39
Beef heart	5	7.9	8.1	7.7	7	19	49	31	29	2.1	1.8	24.3	33.4	—101

* 0.4 Gm of choline chloride per kilogram per day

† 0.8 Gm of choline chloride per kilogram per day

venously as dextrose The protein varied from 4 to 10 per cent of the total calories, while from 9 to 15 per cent of the calories was present as fat The dogs received a mean of 88 calories per kilogram of body weight per day (table 3)

The mean concentration of fatty acids in the liver was 30.9 Gm per hundred grams before the period of feeding and 15.5 Gm per hundred grams after the

period of feeding, a reduction of approximately 50 per cent during the carbohydrate feeding period of fourteen days

The concentration of hepatic glycogen in these dogs averaged 54 Gm per hundred grams in the presence of obstruction of the common duct and the high fat content

b High Carbohydrate Regimen plus Choline Chloride A second group of dogs with fatty livers and obstruction of the common duct was placed on a high

TABLE 3—High Carbohydrate Diet

Dog	Weight, Kg			Days on Diet	Calories			Cal / Day	Hepatic Glycogen Gm / 100 Gm		Hepatic Fatty Acids Gm / 100 Gm		
	Initial	At Operation	Terminal		Protein, %	Fat, %	Carbohydrate, %		At Operation	Terminal Level	At Operation	Terminal Level	Change
S1	30	72	54	14	6	9	85	86	10	61	40.8	15.7	-61
S2	70	70	57	14	10	15	75	112	22	38	28.0	15.2	-46
S3	60	58	48	14	4	11	85	70	25	39	28.0	14.9	-47
104	108	100	92	14	10	14	76	89	31	76	26.6	16.3	-39
Average	72	75	63	14	8	12	80	89	22	54	30.9	15.5	-48

TABLE 4—High Carbohydrate and Choline Chloride Diet

Dog	Weight, Kg			Days on Diet	Calories			Cal / Day	Hepatic Glycogen Gm / 100 Gm		Hepatic Fatty Acids Gm / 100 Gm		
	Initial	Operation	Terminal		Protein, %	Fat, %	Carbohydrate, %		At Operation	Terminal Level	At Operation	Terminal Level	Change
222	73	94	83	8	6	9	85	44	0.9	2.3	25.4	13.3	-48
273	70	54	50	8	6	9	85	76	0.8	2.6	19.1	14.9	-22
224	50	83	80	8	8	12	80	76	1.5	2.4	53.8	33.3	-38
226	72	72	70	8	8	12	80	87	2.1	1.8	22.1	14.3	-35
Average	66	75	71	8	7	11	82	71	1.3	2.3	30.1	18.9	-36*
204	60	68	58	7	9	12	79	78	2.7	4.6	21.2	9.4	-56
310	60	74	71	7	6	8	86	33	4.1	4.2	17.4	11.7	-33
309	90	84	80	7	7	11	82	50	3.4	4.3	25.6	19.3	-25
303	77	97	90	7	3	6	90	20	2.9	3.4	14.0	9.4	-32
205	75	84	71	7	8	10	82	45	2.4	1.1	19.6	16.1	-18
313	64	58		7	4	6	90	35	1.8	2.2	13.3	11.1	-17
312	74	78	66	7	4	6	90	31	2.1	0.9	17.7	14.1	-21
Average	71	78	72	7	6	8	86	42	2.8	3.0	18.4	13.0	-29†

* 0.4 Gm of choline chloride per kilogram of body weight per day

† 0.8 Gm of choline chloride per kilogram of body weight per day

carbohydrate diet, and, in addition, choline chloride was given in doses of 0.4 to 0.8 Gm per kilogram of body weight per day (table 4). When given intravenously or subcutaneously it caused vomiting. It was given most satisfactorily in a meat capsule. The low caloric intake of some of these dogs was due to anorexia and vomiting.

The addition of choline chloride to the carbohydrate diet should, we believe, be effective under the conditions of our experiment, result in a marked reduction in the concentration of fatty acids in the liver. In the rat, in the presence of a high concentration of hepatic lipid, choline chloride causes a rapid reduction of this concentration.

It was our opinion that if choline chloride exerted a marked lipotropic action in the presence of ductal obstruction, when given with a high carbohydrate

diet it might cause as great a reduction in hepatic lipid concentration in seven to eight days as the high carbohydrate diet alone was capable of doing in fourteen days

In the group of dogs receiving 0.4 Gm of choline chloride daily and a mean intake of 71 calories per kilogram per day, the mean reduction in concentration of fatty acids in the liver was 36 per cent. In the dogs receiving 0.8 Gm of choline chloride daily but whose mean caloric intake was but 42 calories per kilogram of body weight the mean reduction was but 29 per cent. When large amounts of choline chloride are given to a dog with obstruction of the common duct, nausea or recurrent vomiting may prevent acceptance and retention of an adequate caloric intake. Although choline chloride would appear to have exerted some hypotonic action in these experiments, a suitable high caloric diet would have resulted in a more significant decrease in the lipid concentration.

c. *Mixed Diet* The dogs in this group received approximately half of their total calories in the form of carbohydrate and a quarter each as protein and fat. While the protein intake was adequate, the fat intake was high. Bile salts were

TABLE 5—*Mixed Diet*

Dog	Weight, Kg			Days on Diet	Calories			Hepatic Glycogen, Gm /100 Gm			Hepatic Fatty Acids Gm /100 Gm		
	Initial	At Operation	Terminal		Protein, %	Fat, %	Carbohydrate, %	Cal / Day	At Operation	Terminal Level	At Operation	Terminal Level	Change
641	63	73	79	7	29	23	48	61	1.6	1.5	55.0	47.0	-15
642	73	80	73	7	31	27	44	80	1.9	3.4	12.4	9.2	-27
647	67	72	70	7	25	21	53	45	2.2	2.2	21.6	13.2	-38
648	74	88	86	7	32	26	42	80	3.0	3.0	27.4	11.5	-58
674	87	84	81	7	25	21	53	37	1.7	0.6	27.4	17.0	-34
675	77	74	73	7	31	26	43	70	1.3	3.8	17.2	10.3	-40
579	100	122	117	7	32	29	39	90	3.7	2.1	32.2	12.6	-61
Average	77	86	83	7	29	23	46	62	2.2	2.4	27.6	17.2	-39

given with the food, but even so, the animals did not eat well, and the total caloric intake was reinforced by intravenous administration of dextrose.

The data on 7 dogs are reported in table 5. The mean reduction in fatty acid concentration over a seven day period was 39 per cent, which is similar to that obtained when a high carbohydrate diet reinforced with choline chloride was administered. The effectiveness of protein in reducing the fatty acid concentration of the liver in the presence of a high fat intake in the diet is here strikingly illustrated.

Mann and Bollman¹⁵ have indicated that a diet high in meat protein or containing a considerable proportion of meat extractives when given to ductally obstructed dogs results in development of abdominal ascites. While the major source of protein in our diets was casein, there was no evidence in our data that meat protein (beef peptone) increased the incidence of ascites. To 5 dogs we gave a beef heart diet reinforced by intravenous administration of dextrose (table 6). Textbooks on nutrition give analysis of the edible portion of beef heart as follows: water, 62.6 per cent, protein, 16 per cent, fat, 20.4 per cent, and carbohydrate, 1 per cent. The dogs did not eat the diet well, even though they were given bile salts. The total caloric intake was low. Approximately

¹⁵ Bollman, J. L., and Mann, F. C. Experimentally Produced Lesions of the Liver, *Ann Int Med* 5: 699, 1931.

50 per cent of the caloric intake was in the form of fat. In only 1 dog was there a reduction in the concentration of fatty acids, in the other 4 the concentration increased from 41 to 188 per cent during a seven day period. The only dog in which a reduction occurred had a very high concentration of fatty acids in the liver, and the caloric intake, while not high, was adequate. In the remaining dogs the very low caloric intake and the high fat content of the diet were without doubt factors in the increase of fatty acids in the liver.

d High Protein, High Carbohydrate Diet. The animals in this group received 72 per cent of their total calories in the form of carbohydrate and 28 per cent as protein (table 7). The caloric intake per kilogram of body weight was high,

TABLE 6—*Beef Heart Diet*

Dog	Weight, Kg			Days on Diet	Calories			Cal / Kg / Day	Hepatic Glycogen, Gm /100 Gm		Hepatic Fatty Acids Gm /100 Gm		Change
	Ini tial	At Oper ation	Term inal		Pro tein, %	Fat, %	Car boh ydrate, %		At Oper ation	Term inal Level	At Oper ation	Term inal Level	
472	90	94	89	7	20	60	19	57	23	32	57.7	34.2	— 42
441	65	50	49	7	35	47	18	22	05	09	23.9	48.8	+104
443	108	112	110	7	16	46	38	25	25	06	11.4	32.9	+188
447	68	77	75	7	11	31	58	18	23	05	14.2	30.4	+114
448	64	73	65	7	15	63	22	22	29	13	14.6	20.6	+41
Average	79	81	77	7	19	49	31	29	21	13	24.3	33.4	+101

TABLE 7—*High Protein-Carbohydrate Diet*

Dog	Weight, Kg			Days on Diet	Calories			Cal / Kg / Day	Hepatic Glycogen, Gm /100 Gm		Hepatic Fatty Acids, Gm /100 Gm		
	Initial	At Operation			Protein, %	Fat, %	Carbohydrate, %		At Operation	Terminal Level	At Operation	Terminal Level	Change
		Initial	Terminal										
87	76	99	94	7	28	0	72	90	13	43	41.1	19.1	—54
83	73	81	64	7	28	0	72	90	44	94	40.4	18.7	—54
78	90	111	100	7	28	0	72	90	11	70	48.7	27.8	—43
33	100	101	100	7	28	0	72	90	15	74	27.1	11.0	—60
40	72	69		7	28	0	72	90	24	14.9	11.1	4.8	—57
39	60	60	66	7	28	0	72	90	21	12.0	19.8	9.9	—50
31	90	106	103	7	28	0	72	90	14	11.4	16.4	7.0	—57
Average	72	89	88	7	28	0	72	90	21	8.9	29.2	14.1	—54

being approximately the same as that of the dogs on the high carbohydrate diet. There was, however, no fat in the high protein high carbohydrate diet. The protein was in the form of casein and beef peptone. Corn syrup was the source of carbohydrate.

During a period of seven days on this diet the mean fatty acid concentration was reduced by 54 per cent, which is approximately the same as the reduction obtained by a high carbohydrate diet of similar total caloric intake in fourteen days. In several instances the concentration had at this time reached the minimal level obtainable in the liver of the dog. The advantage of a diet of this general type should require no further discussion. Not only is the fatty acid concentration of the liver markedly reduced in a minimal period, but the glycogen concentrations are all at or considerably above, the normal level.

COMMENT

It has generally been accepted that in the presence of obstruction of the common bile duct a high concentration of glycogen in the liver cannot be obtained. The data reported in this paper demonstrate that even in the presence of complete ductal obstruction a high concentration of glycogen can be obtained if a sufficient caloric intake of suitable dietary composition can be maintained. The data in table 8 are given in further support of this.

In this group of dogs the central and left hepatic ducts were ligated, excretion of bile from a portion of the liver being thus stopped. The dogs, however, were passing bile into the intestine from the unobstructed portion of the liver. Their appetites remained good on a diet which consisted essentially of carbohydrate.

TABLE 8—*Partial Obstruction with High Carbohydrate and Intravenous Dextrose Regimen*

Dog	Days on Regimen	Ligated Left Lobe Glycogen, Gm /100 Gm	Right Lobe Glycogen, Gm /100 Gm	Ligated Left Lobe Fat, Gm /100 Gm	Right Lobe Fat Gm /100 Gm
442	19	10.8	10.3	5.2	5.4
889	10	7.8	10.6	5.4	5.6
448	13	11.8	12.5	4.9	5.2
377	11	11.1	10.0	5.4	5.4
460	13	7.0	7.3	6.6	6.0
610	10	20.0	16.7	3.5	3.2
322	11	8.1	10.8	5.7	5.3
Average	12	11.0	11.2	5.4	5.2

After ten to nineteen days the dogs were killed, and pieces were removed for analysis from the right and left lobes of the liver. While the concentration varied slightly, the mean concentrations of glycogen and fatty acids were identical. The obstructed portion of the liver contained concentrations of glycogen well above the accepted values for a normal liver, and the concentrations of fatty acids were all low.

These data strongly support our present feeling that too much emphasis has been placed on intravenous administration of dextrose to jaundiced patients and too little on the oral intake of food. The common practice of administering 3,000 milliliters of a 5 per cent solution of dextrose each day and paying no attention to oral intake is, in our opinion, a great mistake. The patient receives from the injected dextrose only 600 calories, which is little more than a third of the basal metabolic requirement. If the glycogen content of the liver is to be increased significantly, carbohydrates and other foods must also be given by mouth. The dextrose administered by the intravenous method spares the patient's own tissues to the extent of 600 calories. Since fat is burned in the presence of carbohydrate, the major body foodstuff which is spared by this method is protein. To the extent that carbohydrates given by mouth

displace liver fat and spare liver protein the liver will be protected against the effect of certain hepatotoxic agents. This concept of Goldschmidt Vars and Ravdin^{7a} throws new light on the beneficent action of a carbohydrate diet in protecting the liver from injury by volatile anesthetics.

The statement made repeatedly in clinical literature that a carbohydrate diet will permit the liver to regenerate more rapidly than any other diet is open to serious question. Regeneration of degenerated parenchymal cells requires protein either endogenous or exogenous. The addition of adequate protein in the diet therefore takes on a new significance. Goldschmidt, Vars and Ravdin^{7a} have shown that protein offers some degree of protection to the liver against necrotizing anesthetics, in adequate amounts it is a powerful lipotropic agent, and an adequate store of reserve protein will facilitate more rapid cellular regeneration.

A great many patients with disease of the biliary tract are obese and have abnormal amounts of fat in the liver. We believe that reduction in the lipid stores of the liver is an important part of the preparation of these patients for operation. The total caloric intake is of importance in evaluating experiments of this type. The high protein, high carbohydrate diet and the high carbohydrate diet provided approximately equal calories for the dogs, but the addition of adequate protein to the diet resulted in a similar reduction in the hepatic concentration of fatty acids in half the time.

The basal caloric requirements of the normal dog have been found to be approximately 45 calories per kilogram of body weight per day. Cowgill has shown that 70 calories per kilogram per day is sufficient for maintaining growing dogs over a long period. Using only those animals receiving 70 or more calories per kilogram per day the high protein, the high carbohydrate diet remains the most satisfactory in reducing the concentration of fatty acids in the liver (table 9).

When the total caloric intake was well below that necessary for basal requirements the fatty acid concentration of the liver increased. The exception to this was in the group given choline chloride, in which a decrease was found with caloric intakes slightly below the basal requirements for energy. Choline chloride, therefore, does act as a lipotropic substance under these adverse nutritional conditions. The concentrations of the glycogen in the liver in some of the choline chloride experiments, especially when the caloric intake was exceptionally low, suggests that choline chloride in some manner protects the glycogen stores of the liver. Data which are soon to be published from the laboratory further support this concept.

The data in table 9 suggest that when the caloric intake is sufficient (70 calories or more per kilogram per day) and adequate amounts of carbohydrate and protein are included the diet can contain a fairly large amount of fat without resulting in fatty infiltration of the liver. This

again stresses the importance not only of the total caloric intake but of the amount of carbohydrate and protein in the diet

In numerous instances we have confirmed experimentally the observations of Goldschmidt, Vais and Ravdin^{7a} that high concentrations of glycogen and fatty acids may be present in the same liver, thus providing exceptions to the Rosenfeld hypothesis¹²

If data such as we are here reporting can be translated to the preparation of the patient with obstruction of the common duct, the following facts must be kept in mind. An adequate caloric intake cannot be achieved at present by any type of intravenous alimentation. If the oral route is impossible the intravenous method should be utilized, but if there is no contraindication to oral administration of foodstuffs the oral route should be used. There is, in our opinion, no special virtue in intravenously injected dextrose over dextrose absorbed from the

TABLE 9—Summary of Data on Dogs Taking Seventy or More Calories per Kilogram of Body Weight per Day

Diet	No of Dogs	Weight, Kg			Days on Diet	Calories			Cal / Day	Hepatic Glycogen, Gm /100 Gm		Hepatic Fatty Acids Gm /100 Gm		
		Initial	At Operation	Terminal		Protein, %	Fat, %	Carbohydrate, %		At Operation	Terminal Level	At Operation	Terminal Level	Change
High protein carbohydrate	7	7.2	8.9	8.8	7	28	0	72	90	2.1	8.9	29.2	14.1	-54
High carbohydrate	4	7.2	7.5	6.3	14	8	12	80	89	2.2	5.4	30.9	15.5	-48
Mixed	4	8.1	9.1	8.2	7	32	26	42	75	2.5	3.1	22.3	10.9	-31

intestinal tract. We are aware of the fact that Soskin and Hyman¹⁶ are not in agreement with this concept.

The administration of bile salts and the vitamin B complex will be helpful in overcoming anorexia and promoting a more normal gastrointestinal activity. A patient whose total caloric intake is inadequate should have little or no fat in the diet. When the total caloric intake is ample, fat can be given provided the diet contains sufficient protein. Since the patient with obstruction of the common duct does not tolerate fat well, the fat content should be kept as low as possible. Even lean meat may contain considerable fat. This must be kept in mind in arranging a diet.

We have found that the aid of a skilled dietitian is exceedingly helpful in arranging diets for the individual patient. This can best be done by consultation between the patient and the dietitian, so that likes and dislikes can be taken into consideration.

16 Soskin, S., and Hyman, M. Physiologic Basis of Intravenous Dextrose Therapy for Diseases of the Liver, Arch Int Med 64 1265 (Dec) 1939

For the occasional patient it may be advisable to use the method of orojejunal feeding recommended by Stengel and Ravdin¹⁷ in order to introduce sufficient amounts of the necessary foodstuffs.

That a diet in which 75 to 80 per cent of the total calories come from carbohydrate and 20 to 25 per cent from protein will prove to be the most satisfactory diet seems highly likely. A minimum of the protein should be provided as meat. Such a program would fulfil the requirements laid down by Goldschmidt, Vars and Ravdin^{7a} and would support Channon's¹³ observation that in the rat on a diet in which more than 14 per cent of the total calories are obtained from protein marked lipotropic action is observed. The administration of choline chloride to man would, in the light of our animal experiments, require enormous doses and might well lead to persistent nausea and vomiting, thus affecting fluid and electrolyte balance in desperately ill patients.

SUMMARY

A high fat content of the liver was found in about one third of a group of dogs on a normal diet which were killed from thirteen to thirty-five days after complete obstruction of the common bile duct.

Dogs were given a high fat diet for two weeks to raise the hepatic concentration of fatty acids. They were then subjected to complete obstruction of the cystic and common ducts. Various diets were compared as to their efficiency in lowering the hepatic fatty acid concentration in the presence of obstruction of the common duct.

A diet high in protein and carbohydrate, with no fat, was found most effective in reducing the fatty acid concentration of the liver and in increasing the hepatic glycogen in the presence of obstruction of the common duct. This diet gave approximately the same result as the usual high carbohydrate diet in about one-half the time.

An adequate caloric intake is an essential part of the preoperative treatment of the patient with disease of the biliary tract. If the caloric intake is low, it is especially important that the diet contain no fat.

The lipotropic effect of choline chloride was demonstrated in dogs with a low caloric intake.

CONCLUSIONS

It is believed that the data obtained in these experiments when added to the observations of Goldschmidt, Ravdin and Vars^{7a} are sufficiently conclusive to warrant the adoption of a high protein, high carbohydrate, no fat diet in the preoperative preparation of the seriously ill patient with disease of the biliary tract.

¹⁷ Stengel, A., Jr., and Ravdin, I. S. The Maintenance of Nutrition in Surgical Patients with a Description of the Oro-Jejunal Method of Feeding. *Surgery* 6: 511, 1939.

PREOPERATIVE AND POSTOPERATIVE CARE IN ANORECTAL SURGERY

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Prior to any operation, it is important that the patient be given a description of the disease, its prognosis and the treatment to be employed. The patient's obligations in respect to the part which he is to play in the course of treatment should be outlined. He should be informed of the probable length of his stay in the hospital and of the amount of time to be spent under the physician's care after dismissal from the hospital. The gravity of his problem should not be minimized. A fissure may appear trivial to every one except the person who is its host. To him it presents a grave problem, and a physician makes a serious mistake when he tells such a patient that hospitalization is unnecessary and that the problem is simple. Often the physician and the patient are both disillusioned later, when it is found that after some simple treatment the lesion is still unhealed and the patient must be sent to the hospital.

PREOPERATIVE CATHARSIS

Patients react in various ways to catharsis, therefore, it is unwise to prescribe a routine medicament for evacuating the bowel. It is almost customary for patients to be given castor oil in preparation for rectal operations. Some patients who take cathartics will empty the colon completely, and when the catharsis is followed by cleansing enemas several days may elapse before sufficient material will accumulate in the colon to provoke another evacuation of the rectum. In some cases a pre-operative cathartic sets up in the colon an irritative reaction which may persist for several days. This may provoke a constant desire to empty the rectum and it may become necessary to use sedatives in order to protect the wound from a constant discharge of intestinal content. Therefore, as a rule it is preferable to cleanse the rectum with one or two saline or soapsuds enemas prior to the operation. If an extensive operation is required it may be well to give the patient a nonresidue diet for a day or two, and by the time the operation is to be performed the colon can be emptied entirely. I have found this to be a very useful scheme, by continuing a nonresidue diet after operation I have been able to carry patients for three weeks or more without the necessity of a bowel

From the Section on Proctology, the Mayo Clinic

movement. Such patients have three meals a day and do not complain of even as much as a gas pain. A suitable nonresidue diet can be provided by any efficient dietitian.

At the Mayo Clinic the operative schedule is carried out in the afternoon. It is the custom to admit patients to the hospital at 9 a. m. They may have a light breakfast usually coffee or tea, orange juice and a slice or two of toast. Immediately on arrival in the hospital a dose of $1\frac{1}{2}$ grains (0.1 Gm.) of pentobarbital sodium (nembutal) is given orally. As has been stated, the rectum is cleared with one or two saline or soapsuds enemas and the patient rests in bed for an hour or two. About two hours later another dose of pentobarbital sodium, $1\frac{1}{2}$ grains (0.1 Gm.), is given, and another small enema is administered. One half hour before the patient is sent to the operating room he is given a hypodermic injection of morphine sulfate. The size of the dose depends on the size of the patient. Sometimes atropine sulfate is added.

ANESTHESIA

Many types of anesthesia may be used in proctologic operations. My associates and I have found block anesthesia of the sacral nerves very satisfactory, low spinal anesthesia has been acceptable in certain cases. Much has been written on this subject by experts, and I suggest that current publications be sought for information along this line.

EXPOSURE OF THE FIELD OF OPERATION

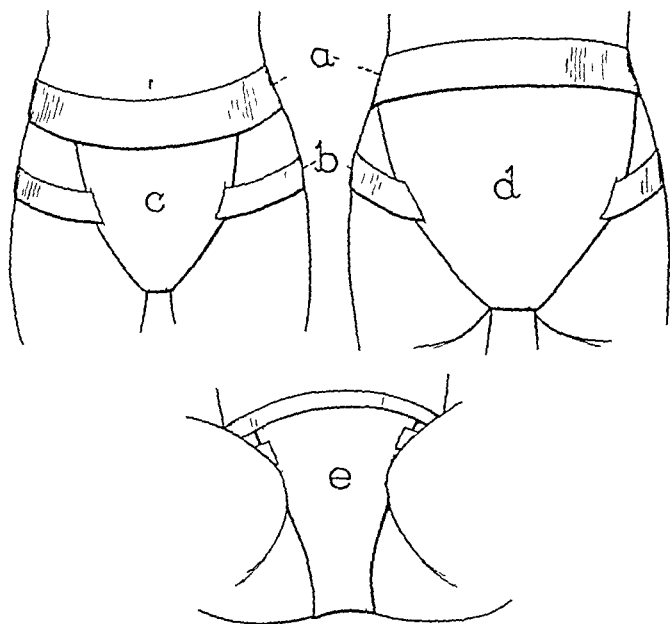
After the patient has been prepared for operation, suitable exposure of the field must be provided. Poor exposure may completely frustrate the surgeon's efforts, whereas his abilities are greatly increased if he is able to bring readily to his hands the tissues on which operation is necessary.

For this purpose the patient is placed in a suitable position on the operating table. Although this position has been referred to in earlier writings, I shall again describe it in detail. The operating table is covered with a sponge-rubber pad thick enough to insure the patient's comfort. At the head of the table there are wings, which are similarly covered and which are arranged so that the patient's elbows may be spread out on them. In approximately the middle of the table, beneath the pad is placed an ordinary elevating bar such as is used for operations on the kidney. The patient is placed in a prone position, and the pelvis is raised to a suitable height by means of the elevating bar. A sheet with a suitable perforation provides sufficient exposure for the operation. The assistants and the instrument nurse may assume satisfactory positions at the table. All operations in the region of the anus, perineum, rectum or sacral region can be performed with the patient placed in this manner.

POSTOPERATIVE CARE

After the operation has been completed, dressings are applied. For many years the T binder has been used to maintain these dressings in place, and for an equal number of years it has been an abomination in the hands of all who have employed it. I shall describe a substitute which I have found useful (see accompanying illustration).

The binder consists of a substantial but soft elastic belt and a supporting portion made of a material which is also elastic. This support stretches in only one direction, and by attachment of the material to the belt in a certain way active pressure is provided in the region of the sacrum, perineum and pubes. Therefore, in addition to maintaining the



Dressing binder *a*, soft elastic belt, *b*, soft elastic lateral straps, *c*, anterior support, *d*, posterior support, and *e*, perineal support

dressings in position, the support adds pressure which gives comfort to the patient, especially when he becomes ambulatory. It renders unnecessary the use of adhesive tape and bandages.

The binder must be carefully fitted to each patient before he arrives in the operating room. This is important. As soon as the patient is placed on the operating table, the binder is drawn down around the knees, so that when the operation is complete the dressing can be applied and the support can be quickly brought into place.

After the operation has been completed, the patient is transferred to bed and is instructed to lie face downward until the surgeon makes his rounds, one or two hours later. Then the condition of the patient is observed, and he is permitted to lie on either side unless there is

some contraindication. Liberal doses of morphine sulfate may be administered, if necessary, to control the pain. The amount of the dose should be governed by the pulse rate and by the weight of the patient. Painless convalescence should not be expected. During the twelve to fifteen hour period immediately following the operation every effort should be made to allay the patient's suffering. As a rule, one or two hypodermic injections of morphine sulfate, $\frac{1}{6}$ grain (0.01 Gm) each for small persons and $\frac{1}{4}$ grain (0.016 Gm) each for those who are larger, are required. Sometimes more than two hypodermic injections of morphine sulfate are necessary, and just as often one injection is all that is needed.

As soon as sensation returns, and not before the application of hot packs is begun. At this time the support is removed together with all dressings except those necessary to protect the wound itself. The hot applications are continued until the patient goes to sleep or until he prefers that they be stopped. The applications should be as hot as the patient can tolerate, and, therefore, it is important that the patient's judgment should not be impaired by any lack of normal sensory reaction of the parts. Accordingly, the physician should be sure that all anesthesia has disappeared before heat is used.

There is an art in preparing and applying hot wet dressings. They are valueless when improperly employed. By placing moistened gauze against the wound and applying over it a rubber insulated electric pad equipped with a switch with which the patient can regulate the amount of heat, one is enabled to change the dressings less frequently than when the old-fashioned hot water bag is used. Gauze moistened with warm hamamelis water (witch hazel) is applied to the anal margins and the perineum as soon as it is of a temperature which the patient can tolerate. A turkish towel is then rung out in hot water and applied, and against this the insulated electric pad is placed. A rubber sheet is used to protect the bed clothing, and a pillow is placed in order to keep everything in position. These dressings are changed sufficiently often to keep the gauze moist, and at each changing it is advisable to ask the patient if he wishes to shift his position before the next dressing is applied. In this way soreness and aching of the hips and lower extremities can be avoided. An additional advantage of this regular change of dressings is the opportunity afforded to inspect the wound.

One of the most important purposes of hot wet dressings is to control the infectious process, which never can be disregarded after such operations. When the wound is beginning its reparative process, these dressings have great value. They may be used for about two hours each morning and each afternoon. In those cases in which abscess sloughing or excessive infection of any type has been a feature these

applications are made more frequently and over a longer period. Other medicated solutions may be employed instead of witch hazel. Metaphen (aqueous solution, 1:200) is of value.

CATHETERIZATION

It is not often necessary to catheterize the patient, although many will find it difficult to urinate without extra effort. Muscle spasm is usually manifested after anorectal operations and is severe in many instances. Many patients who have emptied the bladder just before going to the operating room (this should be routine procedure) and who normally void only once or twice during the day will experience a desire to urinate shortly after the operation. If such a patient is merely provided with a urinal, such a psychologic state will probably develop that catheterization almost surely will be required. If this same patient is informed that it is not necessary to worry and that if he normally voids only once in eight to ten hours there will not necessarily be any change in this program, usually he will rely on this information, and the consequent relaxation, together with sedatives and hot applications, may solve his problem.

It is well to advise the patient to drink sufficient water to satisfy his thirst. If he avoids drinking water because of fear that he may not be able to empty the bladder, the small quantity of urine which accumulates will be more concentrated than otherwise and therefore more provocative of the desire to urinate. The patient should be relieved of all responsibility and should understand that he will be kept under careful observation and that catheterization will be performed and repeated as often as necessary. Many patients will pass through the entire night (twelve to eighteen hours) and then void without difficulty. On the other hand, an occasional patient may be so uncomfortable that he must void within two or three hours after operation. The reaction of each patient must be observed, and the proper procedure must be determined in each case. It is unwise to permit a patient to go longer than eighteen hours without urination, and occasionally it is a mistake to allow him to go as long as that. The symptoms, the intake of water, the interval since the last voiding, the condition of the bladder and the amount of distention as determined by palpation of the lower portion of the abdomen should determine the course of action.

POSTOPERATIVE INTESTINAL HABITS, DIET AND LAXATIVES

After uncomplicated anorectal operations the patient is allowed to have regular meals without interruption. During the first day the food is limited to a nonresidue diet, but thereafter the patient is allowed a "regular" diet. Many patients do not wish to eat because they fear having

a bowel movement. The sooner this situation is discovered the better, for no patient worries as much as the one who finds after several days that he has not had a bowel movement, and he usually requires a laxative before his bowels will move. If he eats three meals a day, the accumulation in the rectum will occur in its normal cycle and will perform a significant part in regulating evacuation of the bowel. In the average case my associates and I prefer that evacuation should not occur in the first forty-eight hours. This is accomplished merely by informing the patient of our wishes. In some instances dysentery may develop, and then it is necessary to establish dietetic precautions and to administer camphorated tincture of opium U S P (paregoric) or a similar medicament to quiet the bowel. On certain occasions, especially after more extensive operations have been performed, we prepare the patient by keeping him on a nonresidue diet for several days before the operation. Even then, however, it is not often necessary to use artificial means to keep the bowels from moving.

On the first or the second postoperative day a small rubber tissue drain which was inserted at the time of operation is usually removed. Sometimes this stimulates action of the bowel, but in most cases the bowel does not act until approximately seventy-two hours have elapsed.

Most patients who have anorectal disease are constipated, and we find it necessary to give them something to regulate the habits of the bowel. For this purpose we make use of substances like agar, which add bulk to the materials which pass through the intestinal tract, and after these materials have been emptied from the rectum there is usually no residue. It is well to avoid the use of laxatives which stimulate bowel movements. When such measures become necessary, enemas are preferable. These clear the rectum satisfactorily, and afterward there is no necessity for further evacuation. Even the mild laxatives sometimes force a patient to go to the toilet several times, and this is undesirable. Many surgeons prescribe liquid petrolatum after rectal operations. The oil, mixed with fecal discharges, soon reaches the rectum and is discharged through the outlet. It is then impossible to keep the parts clean, and consequently the wound remains in an unhealthy and inflamed state. When the bowels begin to act the evacuation should be followed by irrigation of the anus and rectum. This cleanses the wound of fecal and purulent discharges and should be followed by the application of suitable dressings. If the patient has been unable to defecate after seventy-two hours, the wound should be cleansed and dressed anyway. Cleansing irrigations may be of plain, warm water or medicated solutions at 110 F (37.7 C). A small rubber catheter which has been well lubricated is used in place of the ordinary enema tip. Only 2 to 3 inches (5 to 8 cm) of the catheter should be inserted into the rectum.

The length of the patient's stay in the hospital is determined by the extent and character of the operation and the necessity of instituting such measures as cannot be carried out elsewhere. The wound is cared for each day until it is entirely healed or until it is in such condition that it can be cared for by the patient unassisted. Management of the wound is much the same as that necessary for any infected wound. Each day, after evacuation of the bowel and the irrigation just described, the physician should cleanse the anal canal and the wound by irrigation. This is accomplished with an ordinary 30 cc syringe, a connecting rubber tube and a catheter or a perforated irrigating tip. Many irrigating solutions, such as witch hazel, metaphen (aqueous solution 1:200), saturated solution of boric acid or dilute potassium permanganate solution, may be used. If the wound is sensitive, some sedative dressing powder like ethylaminobenzoate U S P provides comfort. Finally, a piece of cotton or gauze of suitable size is tucked into the orifice of the anus or into the margins of the wound. The care of wounds varies from day to day, and it is necessary to employ different methods after different operations. Often the gauze or cotton used for dressings may be saturated with iodoform, dichloramine-T or dilute solution of sodium hypochlorite U S P. When the wound is observed daily, measures can be adopted for the control of any unfavorable condition as soon as it develops.

Sometimes the patient complains of a sense of pressure within the rectum or of undue soreness. The problem may be clarified when examination with a small anoscope reveals that the rectum is full of feces. Such soreness may be due to sutures that have not been absorbed.

The patient should be trained to take care of himself. He should know that the water for irrigation should be between 105 and 110 F (40.6 and 43.3 C), and as a precaution against scalding he should be instructed to place his hand in the water before beginning the irrigation. The irrigation can be conducted while the patient is seated on the toilet. He should be informed that the water is not injected in order to produce evacuation of the bowel but only to cleanse the lower part of the rectum, the anus and the margins of the wound after they have been soiled. When a patient so instructed leaves the hospital, there is little doubt that the wound will be kept clean. After dismissal from the hospital, in addition to the care which the patient gives himself, he should report for daily treatment by the physician until the condition of the wound warrants final dismissal from professional care.

PREOPERATIVE AND POSTOPERATIVE TREATMENT OF TOXIC GOITER

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ST. LOUIS

Toxic goiter is as different in its various clinical manifestations as it is in its pathologic appearance. The young person with an acute fulminant exophthalmic type of thyroid disease often resembles but slightly the much older patient with a mildly toxic nodular goiter who presents a cardiac or a nutritional problem. Indeed this marked discrepancy in clinical types has led many to assume the existence of at least two separate clinical entities, exophthalmic goiter on the one hand and nodular toxic goiter on the other hand. In the United States, Plummer and Boothby have been strong adherents to this dualistic conception. There are others who feel that the varied manifestations of thyroid disease represent different reactions on the part of the patient to the same basic pathologic process. Von Bergmann, one of the enthusiastic supporters of this so-called unitarian conception, has recently made an effort to show that there is a transition from a normal, healthy person to a patient with chronic exophthalmic goiter. He has pointed out that the symptoms of exophthalmic goiter are exaggerations of normal physiologic processes.

Time does not permit me to enter here into a discussion of the merit of either of these two conflicting opinions. However, it seems safe to say that so far as surgical principles are concerned similar basic factors appear to be involved. While it becomes obvious, therefore, that preoperative and postoperative care cannot be standardized to fit all patients, there are certain physiologic principles that hold true, owing to the fact that all persons with these conditions are suffering from an alteration in thyroid function. It should be remembered that the "thyroid patient" must be considered individually, and therapeutic measures must always be undertaken with this constantly in mind. After the surgeon has made his decision that a portion of the thyroid gland must be removed, the problem becomes one of directing therapy in such a way that this operative procedure can be done as safely and as completely as possible.

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PREOPERATIVE CARE

In most surgical conditions preoperative care consists in preparing the patient to withstand the trauma of operation. When relatively normal metabolism exists, this usually resolves itself into a question of ability to withstand a certain amount of tissue injury, loss of blood and fluid and anesthesia. When these factors are kept at a minimum the surgical risk remains slight. When the metabolism is markedly altered as it always is with toxic goiter, the effect of a simple trauma may be magnified many times. There is perhaps no other surgical lesion with which greater care must be taken, therefore, to protect in every way possible the physiologic and biochemical processes which are altered by metabolic upset.

Preoperative care must first be directed at lowering the metabolic requirement of the patient and at restoration toward the normal level of those physiologic and chemical functions that have been grossly altered by the progress of the disease. This treatment may be divided roughly into three different phases—rest, administration of iodine and diet.

Rest—The most effective physical rest is rest in bed. This is true not only because of the marked decrease in caloric requirement but because of the particular features of muscle metabolism in patients with toxic thyroid disease. Fatigue is one of the prominent symptoms of a patient with a toxic goiter. Morphologic changes in muscle are not uncommon in patients with far advanced disease. I have seen patients in whom the muscles of the neck showed remarkable atrophy and replacement with fat. There have been numerous reports of such muscular changes. Means¹ has called attention to the fact that among persons with an elevated basal metabolic rate the increase in blood flow after muscular work is much greater in thyrotoxic patients than in normal healthy persons. Similar conclusions have been reached by other observers. Means has estimated "In terms of actual work performed per unit of time a metabolic rate increase of 65 per cent provided there is no shift in mean blood pressure will impose about the same burden as the mean blood pressure of 200 mm. of mercury." Rest in bed, then, becomes a very important preoperative measure because of the lowered caloric requirements on the part of the body, because of protection of the musculature from fatigue and, finally, because of the relief from the burden thrown on the cardiovascular system by this unusual relation between muscular exertion and the volume of blood flow.

Besides physical rest, great care must be taken to provide the patient with mental relaxation. In recent years the psychotherapist

¹ Means, J. H. *The Thyroid and Its Diseases*, Philadelphia, J. B. Lippincott Company, 1937.

is playing a greater part in the medical care of toxic thyroid disease. In the preoperative treatment of this condition, however, hardly sufficient time exists for much to be done along such lines. By the use of ordinary care and simple means, however, combined with sound judgment of the patient's personality, much can be accomplished by the attending physician. The patient should be placed in a cheerful room or in a ward well away from patients who are ill or who would tend to cause depression. The patient's petty comforts and whims must be catered to. Visiting friends and relatives must be selected with great care, and visits must be made extremely short. Forms of occupational therapy may be instituted. Detailed discussions of the patient's condition should not be done within hearing distance. The tendency to misinterpret chance remarks is often great. When a reasonable degree of emotional tranquility has been established and it seems justifiable, the surgeon, in a casual manner and as briefly as possible, may inform the patient that some day he intends to remove the thyroid gland but that he would rather not mention the exact date lest it cause worry. Most patients prefer not to know the exact date on which they are to be operated on. It is well to think of the emotional reactions of such a patient in terms of epinephrine response. There is nothing more detrimental to the welfare of a patient with toxic thyroid disease than administration of epinephrine either by the physician or spontaneously by the patient. Certain patients going to an operating room in a highly emotional state become "serious operative risks."

Of the various sedatives, the most satisfactory are the barbiturates. Daniels² has recently characterized the action of barbiturates as directly antagonistic to the effect of thyroxin on the midbrain. He cited a considerable amount of experimental and clinical evidence in support of this conception. Whether or not this is true, it is a well established fact that barbitol hypnosis tends to lower the oxygen consumption in an animal. This is in direct contradistinction to the effect of morphine which has a tendency to elevate the basal metabolic rate. Perhaps the most popular of the barbiturates used in cases of toxic goiter is phenobarbital administered in small doses three or four times daily. Other sedatives of value, particularly for patients sensitive to phenobarbital are chloral and bromide mixtures.

Iodine—Since reintroduction of the use of iodine by Plummer the preoperative treatment of the patient with toxic goiter has been made much easier. It has added a factor of safety to surgery of the thyroid that cannot be reckoned in terms of mortality statistics alone. Many previously inoperable patients can now be treated surgically and the frequency of postoperative complications has been greatly reduced. With

² Daniels, L. P. On the Significance of the Various Phenomena of the Basedow Complex. *Acta med Scandinav* 98:561 1939.

such an important therapeutic measure at one's disposal, it is of great importance that iodine be so administered as to obtain the greatest effect.

Shortly after administration of iodine has been started, a striking change appears in the patient. The heart rate begins to slow, nervousness and apprehensiveness lessen, there is a beginning gain in weight and the patient becomes confident of future well-being. At the same time the basal metabolic rate begins to decrease, and the thyroid gland becomes less vascular and firmer to palpation. This improvement, while rapid at first, begins to level off at the end of the first week. It generally has reached its optimum by the end of the second week. After a week or two during which the patient's progress seems to remain more or less stationary there appears a slow return to the original level, although this is generally never quite reached. These time limits are only relative. Often response is much more rapid, and it is therefore necessary to consider each patient individually and watch his progress carefully. It has been thought by some that this apparent lessening of the effect of iodine is due to refractoriness of the patient toward iodine. Means¹ has expressed doubt of this and among his reasons has cited the effect of withdrawal of iodine at such a time, which is definitely associated with a much more rapid return to the original thyrotoxic state. The question cannot be definitely settled until more is known about the mode of action of iodine. It is safe to say, however, that with rare exceptions the patient with a disturbance of the thyroid stands operation better before this delayed return of symptoms takes place. The original observation of Plummer and his colleagues that surgical procedures on the patient with thyroid disease and toxic symptoms are best tolerated after from ten to fourteen days of iodization still holds true in my experience. I likewise have found no great benefit in changing the method of administration of iodine, namely, approximately 10 minims (0.6 cc.) of compound solution of iodine U. S. P. three times daily. The smaller doses of iodine suggested by Thompson and Thompson,³ while generally effective, occasionally are not associated with as rapid an improvement as are massive doses. Iodine as compound solution of iodine U. S. P. is not greatly superior to potassium iodide or any other available iodine salt, but it is easily obtained and easily administered.

Diet—Every patient with toxic thyroid disease presents a nutritional problem. With those patients in whom the goiter is only mildly toxic this problem may be slight. With the more fulminant type of goiter and with the older patient the nutritional problem becomes of greatest importance. The tissue breakdown exceeds the ability of the body to rebuild. The lower the patient's reserve, the greater the operative risk. The caloric requirement of such a patient is often several

³ Thompson, W. D., and Thompson, P. K. Recent Observations on the Iodine Reaction in Exophthalmic Goiter, *Endocrinology* **14** 293, 1930.

times that of a normal person. Not only must this caloric requirement be maintained, but additional food elements must be supplied to build up the depleted reserves of the body. The need for carbohydrates in the thyrotoxic person is excessive. This is due partly to greatly increased consumption resulting from increased metabolic demand and partly to loss of glycogen as a result of the epinephrine effect. Carbohydrate depletion can often be demonstrated in the liver and it is quite probable that there is likewise a depletion in skeletal muscle and cardiac muscle. As a result of this the patient's diet must contain a considerable amount of carbohydrate in an easily assimilable form. It is likewise well known that there is a considerable increase in nitrogen output in the urine of the patient with toxic thyroid disease. This evidence of increased protein breakdown is likewise apparent in the clinical picture. There is muscular wasting, and often the level of protein in the blood may show reduction. There is a definite disturbance in creatine metabolism. Because of the specific dynamic action of protein it has been suggested that proteins be given sparingly in the diet of such a patient. The specific dynamic action of protein in the patient with toxic goiter differs in no way from the specific dynamic action of such food in a normal person, so far as can be determined. It would seem, therefore, that the bad effect that may ensue from the slight elevation in the metabolic rate caused by administration of protein is more than offset by the good effects of protein on the patient. There seems to be a direct relation between protein metabolism and the ability of the body to store glycogen in the liver. Certainly, in the experimental animal on a high carbohydrate, low protein diet the ability of the liver to store glycogen is not nearly so great as when a high carbohydrate, high protein diet is given. The thyrotoxic patient seems to tolerate fats well. Therefore, no especial attention need be given to the fat in the diet except to guard against the diarrhea that may result from its excessive use.

In recent years considerable attention has been focused on the relation between various hormones in the body and vitamins. In so far as the thyroid is concerned, much of this work is still experimental and difficult to evaluate. This is especially brought out in a review of the subject by Schneider.⁴ There seems to be little doubt that vitamin A reserves are markedly depleted in the presence of thyrotoxicosis. A direct antagonism between the action of vitamin A and thyroid secretion has been suggested by some observers, but the existence of such direct antagonism seems questionable. Wegelin⁵ has recently considered this antagonism exten-

⁴ Schneider, E. Die Wechselbeziehungen zwischen dem Schilddrüsenhormon und den Vitaminen, Tr. Third Internat. Goiter Conf. & Am. A. Study Goiter, 1938, p. 439.

⁵ Wegelin, A. C. On the Antagonism Between Thyroxin and Vitamin A, Tr. Third Internat. Goiter Conf. & Am. A. Study Goiter, 1938, p. 431.

sively and the reader is referred to his article for further elaboration. In all probability the most important effect of vitamin A in cases of thyroid disease is related in some way to metabolism of the liver and in particular to glycogen metabolism. Various methods of determining vitamin A insufficiency have been suggested, one of the simplest being the use of the so-called dark adaptation test, which concerns itself with regeneration of visual purple after exposure to bright light. The details of such a study may be found adequately described in a recent article by Wohl and Feldman.⁶ One must therefore include in the dietary regimen the administration of fairly large quantities of vitamin A concentrate.

It has been definitely established for some years that the vitamin B requirement of the body is dependent to a large extent on the metabolic level. When the metabolic rate is increased considerably, as it is in patients with toxic thyroid disease, the ordinary balanced diet is insufficient in vitamin B to take care of bodily needs. There is considerable evidence that most patients suffering from long-standing thyrotoxicosis have a deficiency so far as the vitamin B complex is concerned. This evidence is both experimental and clinical. Means⁷ has called attention to the close similarity of the cardiac abnormalities associated with vitamin B₁ insufficiencies as brought out by Weiss⁸ several years ago and the cardiac manifestations occurring in many patients with thyrotoxic disease. It is more probable that, as Cowgill and his co-workers⁸ have shown, the increased vitamin B requirement is directly the result of an exaggerated metabolic level and the associated utilization of more carbohydrate. Certainly, these patients do better with administration of enormous amounts of the entire B complex as concentrate together with their regular balanced diet. Again it has been suggested by some that there is a direct antagonism between the effect of thyroid secretion and vitamin B. There is evidence that this effect is not a direct one but, as in the case of vitamin A, an indirect one associated with better nutrition on the part of the organism.

Vitamin C relations in cases of toxic goiter are much less pronounced. When the content of the adrenal glands was shown to possess very large amounts of ascorbic acid it was thought that perhaps there would be a definite relation between the thyrotoxic state and vitamin C. This hope has certainly not been realized. Many patients with toxic goiter show a level of vitamin C in the blood that is much lower than normal. Most

6 Wohl, M. G., and Feldman, J. B. Vitamin A Deficiency in Diseases of the Thyroid Gland. Its Detection by Dark Adaptation, Tr. Third Internat. Goiter Conf. & Am. A. Study Goiter, 1938, p. 460.

7 Weiss, S., and Wilkins, R. W. The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, Tr. A. Am. Physicians **51**: 341, 1936.

8 Cowgill, G. R. Human Requirements for Vitamin B₁, J. A. M. A. **111**: 1009 (Sept. 10) 1938.

of the available evidence at present, however, points to association of this factor with the general nutritional level. So far as wound healing is concerned and so far as certain metabolic processes directly related to vitamin C intake are concerned it is important that this vitamin be kept in mind and administered whenever necessary. It has not been my experience, however, to find the definite increase in weight occurring after use of vitamin C that seems to be so apparent after use of the B complex.

In all probability vitamin D is not a great factor. Because of the increased loss of calcium in both the urine and the feces of patients with long-standing thyrotoxicosis it was hoped that this could be alleviated to a certain extent by administration of considerable quantities of vitamin D. However, it cannot be established without question that this loss of calcium is in any way concerned with the metabolism of vitamin D.

In regard to other known vitamins, the data are insufficient to allow any definite opinion to be formed in relation to their action in patients with toxic thyroid disease.

Space does not permit consideration of many of the complications the patient with disease of the thyroid may present. Among such complications, and the most important, is heart disease. Others often seen are hypertension and, at times, apparently true diabetes mellitus with a marked resistance to insulin. Patients with these conditions come into the domain of the internist and require special competence in their handling.

When the preoperative treatment described in the foregoing paragraphs is instituted it does not mean that the patient can be neglected until the passage of a certain amount of time and then be ready for operation. In no condition coming within the surgeon's care is frequent and accurate observation of more importance. The response of the patient to preoperative medication will to a large extent determine the time and the extent of the surgical procedures. In particular care must be taken to observe the change in pulse rate, body weight, blood pressure and basal metabolic rate. Of recent years there has been a growing tendency to deprecate the value of the basal metabolic rate in the diagnosis and study of thyroid disease. The basal metabolic rate when accurately estimated is a fair estimate of the oxygen consumption of the patient. It probably is one of the most important adjuncts in determining the effect of the preoperative treatment. This is especially pronounced in the case of the younger patient. In the patient who has been under treatment with iodine for a long time or in the patient who presents chiefly nutritional or cardiac disturbances changes in metabolic level may not be so pronounced yet they are none the less valuable. With such a patient particular judgment is required in interpretation of these tests. Above all it must be correlated with the whole clinical picture and not used to the complete exclusion of all clinical signs.

As a general rule the wise surgeon will know before operation the extent of the procedure. The surgeon who waits for evidence at the operating table to determine whether he is to do a lobectomy or a subtotal thyroidectomy often finds that this evidence presents itself too late. In the progress of preoperative therapy there are many danger signals that one must take into consideration. Among these are failure of a very great drop in the basal metabolic rate after iodination, continued loss of weight by the patient in spite of the most careful preoperative treatment, psychosis or mental aberration, a very large pulse pressure, heart disease and, above all, advanced age or long-standing toxic goiter. In the presence of the last mentioned conditions one is most likely to be led astray. The lack of emotional reactions, the relatively low basal metabolic rate and a gland that is not extremely vascular and is technically easy to remove may seem to present ideal indications for a single stage operation. In the hands of most surgeons the operative mortality increases with the age of the patient and the duration of the toxicity of the lesion. In the hands of the careful surgeon, therefore, the frequency of multiple stage operations will increase under the same conditions.

POSTOPERATIVE CARE

Postoperative care of the patient with toxic goiter depends largely on the condition of the patient at the time of operation and on what happened to the patient during operation. When a patient is operated on at the optimum time and the proper amount of thyroid tissue is removed with the least possible trauma, one may expect little trouble. The care of the wound will depend on the particular technic used and presents no unusual features. One must always expect an excessive rise in pulse rate after an operation on the thyroid as compared to surgical treatment of other conditions. This is associated with an increased metabolic response. The maintenance of water balance, therefore, becomes an important factor. Particularly is this true when it is remembered that the patient has a certain amount of discomfort on swallowing for the first twenty-four or thirty-six hours. Accumulation of mucus in the throat, which is often troublesome, may be taken care of by steam inhalation and by medication with drugs of the opium group. Care must be used to keep the patient comfortable. Where the environmental temperature is elevated, as it is in many places in the summer, the use of a cooled oxygen tent is often most gratifying. When such a tent is to be used, however, the patient should be informed about it several days before operation in order to prevent the terror experienced by many on awakening from the anesthetic encased in an oxygen tent. The interpretation is always one of impending disaster. The administration of atmosphere containing a high oxygen content is likewise of the greatest value.

Fluids may be administered subcutaneously and intravenously. There are few patients who need less than 4 or 5 liters during the first twenty-four hours after operation. These fluids may be administered as physiologic solution of sodium chloride or intravenously as dextrose in either water or physiologic solution of sodium chloride. Concentrations of dextrose over 5 per cent when given intravenously tend to promote a certain amount of dehydration and should be used only when the need of carbohydrate is great. It is well to place sodium iodide in the intravenous solution when this is given immediately after the operation. The patient should be encouraged to drink highly sweetened fruit juices as soon after operation as possible. Cold drinks and ice cream are often most gratefully received. If the heart rate is considerably increased, cold applications over the head and an ice bag over the chest, as well as cold applications to the extremities, are of great value.

Whenever a postoperative crisis, or storm, develops it may be expected to show evidence of occurring within from four to eighteen hours after operation. It usually manifests itself as an exaggerated postoperative response. There is a marked increase in pulse rate. The patient appears most apprehensive, at times even becoming delirious. There may be gastrointestinal episodes, particularly vomiting and diarrhea. The therapeutic measures to be instituted are those directed at lowering the rate of oxygen consumption of the body and at the same time lowering the emotional reaction of the patient. Large doses of barbiturates or of morphine or even avertin with amylene hydrate given per rectum are often justified. Delirium, excessive fear and thrashing about in bed by the patient must be corrected at all costs. It must be remembered that utilization of water and of sugar is multiplied many times and must be compensated for by constant intravenous drip. Lowering of the body temperatures as has been described is likewise of great value in lowering the metabolic rate. The use of blood transfusion is of great help. This can be administered through the cannula already inserted for the intravenous sugar medication.

Perhaps in no other type of patient is adequate postoperative oxygenation so important. Respiratory difficulty should be corrected at the operating table. There is nothing more dangerous to a thyrotoxic patient after operation than cyanosis. If there is no evidence of tracheal obstruction this cyanosis must be taken care of by immediate use of an oxygen tent. Great care must be utilized in ruling out the presence of hemorrhage beneath the muscles as the cause of such cyanosis. If this is found to be present the wound must be opened immediately and all hemorrhage stopped.

Usually after the first week or so the patient is in condition to sit in a chair. It is well to continue the postoperative administration of compound solution of iodine U. S. P. in the same doses as were given

preoperatively until a week or two after the thyroid has been removed and the patient becomes stable so far as the metabolism is concerned. After this time administration of iodine may be discontinued, and if there are no evidences of overfunction of the thyroid and the basal metabolism is within the normal range it may be discontinued for good. There is still considerable discussion as to the question of postoperative iodine medication. It would seem that if the metabolic level is in the realm of normal and the patient is free from symptoms further iodine treatment would be useless. Iodine for the first few weeks has been given by some with the idea of prevention of postoperative hyperplasia. Such may be the action of iodine, although there is as yet little proof that this is true. If there is mild persistence of thyrotoxic symptoms the administration of iodine for a long period is often justified, and it has been found in the hands of many to be an excellent drug for treatment of the slight thyrotoxic symptoms that sometimes persist after thyroidectomy. After the patient's discharge from the hospital adequate rest must be given until recuperation of the physical and emotional deficiencies that were present before operation has occurred. Dietary measures must be continued and exercises graded very carefully. Later postoperative treatment is generally a matter of common judgment and requires no elaboration. As for treatment of the heart disease so often present in old thyrotoxic patients, the thyroidectomy has been the most important weapon. If the heart disease is such as to demand attention generally, it should be handled in a manner similar to the same type of heart disease in a nonthyrotoxic patient.

If a mild degree of thyrotoxicosis persists after operation it can be corrected in many patients by roentgen treatment of the remaining portion of the gland.

PREOPERATIVE AND POSTOPERATIVE CARE OF PATIENTS WITH SURGICAL DISEASES OF THE CHEST

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Good clinical results in the treatment of surgical diseases of the chest are strikingly dependent on meticulous attention to the many details of preoperative preparation and postoperative care of the patient. Countless patients have failed to recover their health or have died after technically perfect thoracic operations solely because the surgeons failed to apply with intelligent understanding those preoperative and postoperative measures that are based on a thorough familiarity with thoracic physiology and pathology and with the behavior of diseases of the chest.

DIAGNOSTIC AND OBSERVATION PERIOD

As the effect of surgical therapy is intimately linked with the individualistic behavior of many thoracic diseases, the decision as to which patients should be treated surgically, the choice of the most suitable operation and the surgical management of the patient require of the internist or surgeon a deep knowledge of both the medical and the surgical aspects of thoracic disease and the reaction of one on the other. Good clinical results cannot be obtained with satisfactory uniformity by a surgeon who is not familiar with the behavior of thoracic disease unless he has the constant advice of an internist who has had extensive experience with the behavior of thoracic disease under surgical therapy. The danger of a final decision to operate on the basis of a casual consultation about the patient's most recent roentgenogram, without the surgeon's actually seeing the patient, is apparent. Apart from the suitability of a particular phase of a disease for operation and apart from the choice of the proper operation, one of the most difficult tasks facing the internist and the surgeon is to decide whether, in certain cases, the lesions are too extensive for cure or improvement by surgical measures and whether the cardiocirculatory and respiratory systems have sufficient functional reserve to tolerate whatever decrease in reserve the contemplated operation may produce. The scope of this article does not permit a detailed consideration of the complex interplay of the factors that control such decisions which, in the last analysis, must be based on experience.

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Cardiocirculatory disease, including compensated valvular lesions, does not necessarily contraindicate extensive thoracic operations, which, however, should be performed in stages when possible. The electrocardiographic findings and the results of tests of cardiocirculatory competency should be satisfactory. Even early signs or symptoms of cardiocirculatory decompensation or a history of decompensation are relative contraindications to extensive thoracic operations unless the condition to be relieved by operation is the immediate cause of the decompensation. Digitalis should not be given in preparation for operation unless decompensation is present.

The slightest objective (and under certain circumstances, subjective) evidence of dyspnea and cyanosis at rest in bed or after slight exertion is an ominous sign if the contemplated operation is one that would reduce the respiratory functional reserve to an extent that could not be compensated for by temporary postoperative inhalation of oxygen. When dyspnea is questionable in a patient at rest in bed, observation of the behavior of respiration after exercise of the arms or a short walk is valuable, as are the tests of oxygen saturation of the arterial blood described by Whitehead and Miller¹ and the various tests of respiratory function elaborated by Cournand, Richards and Darling². Determination of the function of each lung separately by bronchspirometry has been made by Jacobaeus,³ a number of variations of the method have recently been proposed. Although a low preoperative respiratory reserve is dangerous for many patients on whom thoracic operations are to be performed, the dyspnea attending certain conditions may be relieved by suitable surgical procedures. Among these conditions are pressure on the lung by tumor or by air or fluid in the pleural cavity, displacement of the mediastinal organs with kinking of the trachea, bronchi or great vessels or with torsion of the heart, constrictive pericardial disease, the passage of arterial blood through a large part of a lung that is not being properly aerated because of extensive infiltration or bronchial obstruction, and weakness of the cardiac and skeletal respiratory muscles because of toxic absorption from such diseases as pulmonary abscess and tuberculosis.

Roentgen Examination—The susceptibility of the thoracic organs and their lesions to exceptionally accurate roentgen visualization makes detailed roentgen examination the most important means of diagnosis and of aiding the surgeon in planning the most suitable operative procedure.

1 Whitehead, W. K., and Miller, A. T., Jr. Evaluation of Respiratory Function, *Am Rev Tuberc* **41** 1-11, 1940.

2 Cournand, A., Richards, D. W., Jr., and Darling, R. C. Graphic Tracings of Respiration in Study of Pulmonary Disease, *Am Rev Tuberc* **40** 487-516, 1939.

3 Jacobaeus, H. C. Bronchspirometry. A Review of Present Experiences and Some Further Investigations, *J Thoracic Surg* **7** 235-261, 1938.

A study of changes occurring in the lesion in serial roentgenograms made since the beginning of the illness is of such value in many cases as to justify postponement of a decision about treatment until roentgenograms made in other hospitals have been received. Since in certain types of lesions important changes may occur rapidly, a final decision about surgical therapy should usually not be arrived at unless a roentgenogram made within from one to four weeks is available for study. So important is a thorough roentgen study in many conditions that attempted economy in the number of films made often eventually proves costly to the patient. In addition to a fluoroscopic examination and the taking of anteroposterior stereoscopic film, lateral, oblique and "Potter-Bucky technic" films and, in rare instances, laminagraphs may be necessary for a thorough study of the condition.

Pneumothorax—Preoperative induction of pneumothorax (at the time of removal of pleural fluid if this is present) may give useful roentgen information as to whether neoplasms and other lesions are in the lung, thoracic wall or mediastinum and whether they have invaded structures in which they did not originate. The knowledge of the extent and position of pleural adhesions that a pneumothorax will determine is valuable in certain cases of tumor and of lesions requiring lobectomy or pneumonectomy in helping the surgeon to plan the operation and the best position for the incision. Exceptionally, inspection of the pleural cavity with the thoracoscope and removal of a specimen of tissue for microscopic examination may give valuable diagnostic aid and determine whether pleural metastasis has occurred from a malignant neoplasm.

Bronchograms—The value of intrabronchial instillation of iodized oil followed by the taking of roentgenograms in the demonstration of bronchiectasis and bronchial obstruction is well known, but the danger that the oil may cause an acute and dangerous increase in tuberculous or nontuberculous pneumonitis is less generally recognized. When the lesions are in a labile condition, especially in the presence of a partial bronchial obstruction that causes interference with efficient evacuation of the oil by coughing, the danger is great. The chief conditions in which introduction of oil into the lung may prove dangerous are the acute and subacute phases of pulmonary abscess, an exacerbation within two months of suppurative pneumonitis that is or is not accompanied by bronchiectasis, a labile type of parenchymal tuberculosis, particularly in the presence of a partial bronchial stricture, and partially obstructing bronchial neoplasms with suppuration distal to the obstruction.

The outlining of the important bronchi of one lung usually requires not more than 10 cc. of iodized oil if the oil is introduced by means of

an intratracheal catheter and if large saccular bronchiectases are not present. A greater amount is likely to clog the bronchioles and alveoli (a smaller amount may do so in certain cases), thereby interfering with accurate interpretation of the roentgenograms. Recently retained iodized oil has been found by Mr. Ronald Belsey in the clinic of Mr. J. E. H. Roberts, of London, England, to increase the danger of postoperative pneumonic states after lobectomy and pneumonectomy. The recommendation is therefore made that major operations, unless urgently required, should not be carried out within two months of the instillation of iodized oil if more than traces of the oil have been retained.

Bronchoscopy—Bronchoscopic procedures are rapidly becoming universally recognized as an indispensable diagnostic and therapeutic measure in many thoracic conditions. Bronchoscopic study is superior to bronchographic study for the differential diagnosis of lesions within the visible limits of the tracheobronchial tree. It permits identification and biopsy of a bronchogenic carcinoma or adenoma and accurate determination of the cephalad limit to which the growth has extended. It enables the surgeon to determine the location, size and type of a bronchial stricture, to detect ulcers that may be the sole source of hemoptyses or of tubercle bacilli in the sputum, to localize the segment of the lung containing an abscess by identification of the bronchus from which pus is exuding, to discover foreign bodies that are not opaque to roentgen rays and appropriately to treat these various conditions. Since the interpretation of the bronchoscopic findings and the most appropriate treatment are intimately dependent on a sound knowledge of thoracic diseases, the bronchoscopist should have such knowledge. Ideally, the bronchoscopist for patients on whom thoracic operations are to be done should be the thoracic surgeon who is responsible for the determination of the types of treatment to be used and the best time relation between them.

PREPARATION FOR OPERATION

Postponement of Operation—Although surgical intervention and the type of operation may have been decided on, adequate preparation often makes postponement important, apart from the period needed for diagnosis, observation and a possible trial of nonsurgical treatment. This statement, of course, applies only to those patients whose conditions does not demand prompt operation. The results of surgical treatment will be better in certain chronic diseases if patients who are "run down" are given a preoperative period of rest in bed and adequate diet, if untreated syphilis is treated, if the blood of anemic patients is restored by iron or by a series of blood transfusions, if a "foul mouth" is treated and if the weight of unduly obese patients, especially those who are even slightly

dyspneic, is reduced slowly by proper dieting. Pustular acne or other cutaneous lesions that might result in wound infection should be treated with scrubs with soft soap U S P (green soap), alcohol dressings and roentgen irradiation or other appropriate treatment.

Patients who have been strictly confined to bed for one or more months should be got out of bed into a chair for gradually increasing periods each day until after having sat up for fifteen or twenty minutes, they are not dizzy and the pulse rate is not much faster than when they were in bed. This mild form of exercise "tones up" the cardio-circulatory system together with the vasomotor mechanism, and tends to prepare them for the unusual demands that may be imposed on them by a major thoracic operation. Similarly, most patients who are to have a staged operation should be got out of bed for ten or fifteen minutes on each of the three or four days preceding the second and subsequent stages.

Major operations should not be performed on patients who are menstruating or who are about to menstruate, as some diseases particularly tuberculosis, undergo an accession of activity at this time. Also, extensive operations should rarely be performed during an actively progressive phase of tuberculosis. Operation should be postponed if there has been a recent hemoptysis (provided the severity or duration of the bleeding does not in itself demand surgical measures), because blood retained in the lung may cause, within a week or so, an acute new area of disease which might be aggravated by immediate surgical intervention. Lobectomy or pneumonectomy should not be carried out within two or three months of a flare-up of pneumonitis complicating bronchiectasis.

Postponement of operation is not justified in the case of a strongly suspected carcinoma of the lung of which a definite preoperative diagnosis cannot be made bronchoscopically and by biopsy, presumably because the lesion is in a small bronchus that cannot be visualized bronchoscopically. Since benign thoracic tumors may become malignant or are likely to lead to various complications through pressure and degeneration from increasing size such tumors should be removed even though at the time they are causing no troublesome symptoms.

Interval Between Stages—Sufficient time should usually be allowed between the stages of staged operations for the patient to recover fully from any debility or increase in temperature the previous operation may have caused. The surgeon should make provision for the temporarily lowered resistance to tuberculosis (the "negative phase") that may be assumed to occur after major operations by allowing an interval of not less than three weeks between the stages of a thoracoplasty or other major procedure. In clean wound cases the second and subsequent operative stages should be deferred until infiltration of the

wound has largely disappeared and until the incision is completely healed, dry and without any crust. When the absence of suitable pleural adhesions requires a two stage operation for drainage of a pulmonary abscess, not less than twelve days should be allowed for the gauze packing that has been placed against the parietal pleura to cause firm pleural adhesions. In case air has entered the pleural cavity through a tear of the parietal pleura made at the first stage operation, the second stage should be deferred for at least twelve days after complete aspiration or absorption of the air. In case pleural fluid forms as a result of the gauze packing or of a pleural tear, the same rule as for air in the pleural cavity should be followed.

Aspiration of Air or Fluid from Pleural Cavity—The importance of gradual decompression of a pleural or pericardial empyema cavity by aspirations before surgical drainage is carried out is well known. Positive pressure of fluid or air in the pleural cavity should similarly be reduced before any operation directly involving the pleural cavity, lung or mediastinum.

The greatly increased intrapleural pressure produced by any extrapleural collapsing operation, such as thoracoplasty, in the presence of fluid or air in the pleural cavity exposes the patient to grave danger of cardiorespiratory decompensation. The removal of only two ribs may cause rapid decompensation, especially after the intrapleural pressure is further increased by the variable shift of the mediastinum that occurs when the patient is placed on his back at the conclusion of the operation. In order to avoid this danger, fluid or fluid and air should be aspirated before operation, so that the intrapleural pressure is relatively low at the time of operation. Further reduction of pressure by aspiration may be necessary during or immediately after operation and at intervals thereafter if the pressure should be raised by formation of pleural fluid. When a thoracoplasty is to be performed on a patient with an undrained empyema cavity complicated by a bronchopleural fistula, the intrapleural pressure can usually be counted on to reduce itself during operation owing to the discharge of air through the fistula, any fluid in the pleural cavity of such a patient should, however, be aspirated as completely as possible before operation so as to prevent the forcing of infectious fluid through the fistula into the lung or the drowning of the patient if large amounts of fluid are present.

Evacuation of Pulmonary Secretions—The danger of bronchogenic spread of tuberculosis or of nontuberculous pulmonary suppurative disease as a result of stasis of sputum during anesthesia and during that part of the postoperative period when the patient is unwilling or unable to expectorate effectively is sufficiently great to make important the thorough evacuation of all free tracheobronchial secretions immediately

before operation. A number of cases have been reported in which patients with great amounts of pulmonary secretions from bronchiectasis or abscess have drowned during, or shortly after, operation owing to the occlusion of large bronchi by secretions evacuated from the lesions during the operation. The preoperative measures that should be used to make sure that the lung will be as free as possible of secretions at the time of operation depend on the amount of the secretions and facility with which the patient can voluntarily expectorate them. Patients with abundant secretions from pulmonary abscess or bronchiectasis should use frequent postural drainage for days or even weeks before operation, since the elimination of stasis of secretions tends to reduce the number of secretions formed. For this reason, the intermittent or continuous use of the Trendelenburg position of the bed for several days or weeks before operation and a series of bronchoscopic treatments to shrink swollen mucosa and promote evacuation of secretions are often valuable. Immediately before operation the patient should expectorate all the sputum he is able to and, if necessary, use postural drainage. Bronchoscopy immediately before operation is only rarely advisable.

Miscellaneous Matters—An adequate fluid intake is especially important on the day and night before operation. The teeth should be brushed and a mouth wash used on the morning of operation, so as to reduce the danger of the aspiration of infectious secretions from the mouth into the lungs. Depression of the patient by a heavy sleeping potion should be avoided the night before operation. Large doses of opiates before anesthesia are dangerous because they are generally depressing to the patient and tend to cause abdominal distention and to reduce or abolish the cough reflex during, and for some time after, operation. Atropine should not be given unless there are abundant thin pulmonary secretions or unless ether is to be the anesthetic agent, because atropine makes secretions viscid and, therefore, difficult to expectorate.

ANESTHESIA

Since varying degrees of impairment of respiratory function are caused both by thoracic lesions and by thoracic operations, anesthetic agents that produce the least possible impairment of respiratory function should be chosen when they do not present counterbalancing disadvantages. Assuming expert administration, cyclopropane is probably the best general anesthetic agent, in that anoxemia can be avoided and respiration is quiet. Relatively minor disadvantages of cyclopropane are its narrow margin of safety, the danger of explosion, the moderate delay in the patient's awakening and the occasional period of excitement during awakening. So that the patient will be awake shortly after the completion of the operation, some anesthetists substitute nitrogen

monoxide for cyclopropane during the last fifteen or twenty minutes of anesthesia. Apart from this use of nitrogen monoxide it is inferior to cyclopropane because surgical anesthesia frequently requires that the patient be kept in a cyanotic-anoxic condition, even when 40 per cent oxygen and 60 per cent nitrogen monoxide are used.

Ether given by the drop method is, *per se*, an eminently safe anesthetic, but it increases the amount of pulmonary secretion and produces relatively prolonged sleep or semiconsciousness after completion of the operation, during which time the patient is unable to cough and expectorate voluntarily and efficiently, thereby promoting stasis of infectious secretions in the lungs. Prolonged nausea and vomiting are incidental disadvantages of the use of ether. Intravenous pentothal sodium, together with oxygen inhalation, for operations lasting as long as an hour and a half is an excellent anesthetic agent for patients who have been found to have a prolonged period of vomiting or otherwise to react badly to other general anesthetic agents.

Local and regional anesthesia is excellent for thoracic operations that are not extensive and for some extensive ones, especially when preoperative dyspnea requires that all free pulmonary secretions be expectorated during the course of the operation in order to keep open the lower, as well as the upper, airways. For the same reason, an inhalation anesthetic should be given through an intratracheal catheter to patients having abundant pulmonary secretions that may flood the bronchi during the operation, the catheter may be used to aspirate the secretions from time to time. The use of large doses of avertin in amylene hydrate to supplement other anesthetic agents is dangerous, because this may produce several hours of unconsciousness or semiconsciousness after operation, with resulting possible anoxia and spread of the pulmonary infection from stasis of pulmonary secretions. Avertin in amylene hydrate in a dose of from 60 to 70 mg per kilogram of body weight is useful to supplement nitrogen monoxide anesthesia, as surgical anesthesia can be maintained with less cyanosis than if nitrogen monoxide were used alone. Chloroform is rarely used in the United States. Spinal anesthesia has no important advantages in thoracic procedures over other far safer forms of anesthesia.

OPERATION

Virtually all thoracic operations, whether performed with the aid of local or of general anesthesia, should be carried out with the operating table at 10 or 15 degrees of the Trendelenburg position so as to promote gravitation of pulmonary secretions toward the mouth and prevent aspiration of secretions from the nose and mouth into the lungs. The reverse Trendelenburg position of the table should be used when

empyema with a bronchopleural fistula is being drained with local anesthesia

The routine intravenous administration of dextrose or saline solution or blood during operation is advisable only when prolonged operations, such as removal of large neoplasms, pneumonectomy or lobectomy, are contemplated. In such cases an intravenous cannula or needle should be introduced into the long saphenous vein at the ankle before the operation is begun. A cannula in a vein of an arm is likely to be disturbed by one of the surgeons during operations on the thorax.

After the patient has awakened from general anesthesia and has been placed on his back with the table still in the Trendelenburg position, he should be made to cough until all face secretions have been expectorated or until the surgeon is satisfied that adequately deep coughing will produce no expectoration.

A patient who has had an extensive thoracic operation should, if possible, be transferred directly from the operating table to his own bed rather than to a stretcher. Every patient should have his shoulders and arms protected by a pinned blanket or sheet shawl before he leaves the operating room to journey through relatively cool and draughty halls to his room. A blanket that is merely laid over the patient's shoulders and neck soon becomes displaced, exposing him to dangerous chilling.

POSTOPERATIVE MANAGEMENT

Shock.—True surgical shock may, of course, occur during and after thoracic operations and may be prevented or treated as it is when it occurs from operations on any part of the body. There is, however, a type of shock the signs and the symptoms of which are similar to those of ordinary shock, that is peculiar to thoracic operations and that is subject to special preventive and therapeutic measures. The chief causes of this type of shock are paradoxical respiratory movement of the thoracic wall with resulting cardiorespiratory incompetence and anoxemia, accumulation of secretions in the tracheobronchial tree with resulting anoxemia, exhaustion from labored breathing and frequent ineffective coughing and perhaps atelectasis, and undue pressure on the lung or mediastinum by the too great thoracoplastic collapse of the thoracic wall at any one operative stage, by too large an intrathoracic packing, by too tight a dressing after resection of ribs, by abdominal distention, by accumulation of large amounts of serum in a wound after the resection of ribs or by collapse of the thoracic wall over an intrapleural air or fluid space in which the pressure has not been reduced before operation by aspiration. Exceptionally, "thoracic shock" results from too negative a pressure in a pleural cavity in which the lung cannot expand freely because of stiffness of the visceral pleura. Measures

that are useful in preventing or combating thoracic shock are considered in various parts of this article

Determinations of the pulse rate and blood pressure should be made every fifteen minutes immediately after large thoracic operations and, after an hour or two, at increasing intervals

Intravenous Fluids—The routine intravenous administration of 3,000 cc of fluid (alternately, 1,000 cc of 5 per cent dextrose solution, 1,000 cc of Ringer's solution or of physiologic solution of sodium chloride and 1,000 cc of 5 per cent dextrose solution) after major thoracic operations probably averts, in a considerable number of cases, surgical shock that would be more difficult to manage if the fluids were not given until signs of shock had developed. Furthermore, the fluid provides for a suitable water balance and for excretion of at least 1,500 cc of urine during the twenty-four hours succeeding operation, even if vomiting should prevent the retention of swallowed fluids (Coller and Maddock⁴). If shock should occur and not be controlled by the fluids mentioned or by stimulating drugs, a blood transfusion, blood serum or acacia solution (if the replacement of blood elements is not of primary importance) should be given.

Oxygen Inhalation—In Cameron Haight's and my clinic oxygen is given routinely only after pneumonectomy, lobectomy, removal of large intrathoracic neoplasms, esophagectomy and pericardiectomy. Patients who have had other operations are given oxygen if there is slight cyanosis or an appreciable degree of dyspnea or if there are any signs of shock or even merely a persistently unduly elevated pulse rate. The prompt use of oxygen under these circumstances, although often unnecessary, does much, I believe, to prevent the development of serious complications, especially in "poor surgical risks" with a low respiratory reserve. The simplest efficient method of administering oxygen is by way of a humidifier through an intranasal catheter or a face mask. An oxygen tent is more cumbersome and has the further disadvantages of making nursing care relatively difficult and of alarming certain patients because of their confinement in a small space. The principal advantages of a tent are that its ice-cooled air is valuable to debilitated or febrile patients in hot weather, that a tent avoids the discomfort or irritation of an intranasal tube, of which occasional patients complain, and that the oxygen concentration of the air to be inhaled may be readily determined.

Paradoxic Respiratory Movement of Thoracic Wall—Weakening of the bony thoracic wall by resection or division of the ribs or sternum results in an inward or paradoxic movement of the weakened part of

⁴ Coller, F. A., and Maddock, W. G. Water and Electrolyte Balance, Surg., Gynec. & Obst. **70** 340-354, 1940

the thoracic wall during inspiration and an outward or paradoxical movement during expiration. The underlying portion of the lung undergoes similar paradoxical movements, and a mobile mediastinum swings from side to side as a result of the difference in the intrapleural pressures of the two hemithoraces. The effect of these phenomena is that ventilation and circulation of the lungs are inefficient and anoxemia results. Dyspnea is usually a prominent symptom. The greater the dyspnea, the greater the paradoxical movement, with a resulting vicious cycle. When the condition is severe, the symptoms are labored breathing, cyanosis, rapid pulse, lowered blood pressure and inefficient coughing and expectoration. A state of "thoracic shock" then exists. Obviously, the condition would not have arisen if the number of ribs or the length of ribs removed had been sufficiently restricted to prevent respiratory, and consequent circulatory, decompensation. Measures that are useful in overcoming the condition are administration of oxygen, a firm pressure dressing (preferably applied with adhesive elastic straps) over the area of paradoxical movement, having as its object a reduction of the paradoxical respiratory excursions, the patient's lying on the area of paradoxical movement, which tends to have an additionally stabilizing effect, aiding the patient to evacuate retained pulmonary secretions (see a subsequent section) in order to reduce dyspnea, which in turn reduces the extent of paradoxical movement, blood transfusion, and other measures to combat shock. In cases of exceptionally grave paradoxical movement the use of a Drinker respirator may be life saving.

Aspiration of Air or Fluid from Pleural Cavity—Under this same heading in the section on preoperative care the importance of preoperative aspiration of fluid or air has been discussed. If, however, the signs of thoracic shock should occur during or after a thoracic operation when any air or fluid is still present in a closed pleural cavity, the surgeon should suspect that the intrapleural pressure has been unduly increased by collapse of the thoracic wall. Such an increase of intrapleural pressure may occur when as few as one or two ribs have been removed. The surgeon should, therefore, immediately determine the pressure of the air pocket with a pneumothorax apparatus, and if the pressure is higher than — 5 cm. of water or, in some cases, — 10 cm. of water, he should aspirate air. If fluid but no air is present in the pleural cavity, the intrapleural pressure should be reduced by aspiration of most of the fluid. Since the need for reduction of intrapleural pressure is sometimes urgent, the surgeon should know before operation the exact position, in both vertical and horizontal planes, of an intrapleural air or fluid pocket.

The reduction of intrapleural pressure is equally important in cases in which no air or fluid was present in the pleural cavity before operation but in which air was introduced during operation. Such introduc-

tion of air obviously occurs during any operation in which the pleural cavity is opened, unless the lung is completely expanded by positive intrapulmonary pressure before the parietal pleura is closed, air will be present in a closed pleural cavity. The presence of a considerable volume of air in the pleural cavity may not be suspected in cases in which the surgeon hears only a little hissing of air which is being sucked through an accidental tear of the parietal pleura made in the course of a thoracoplasty or an operation for drainage of an abscess or which is being sucked between the stitches used to close an open incision into the pleural cavity. The rapidity with which a large volume of air can be sucked through such small openings in the parietal pleura is astonishing. Prompt recognition and aspiration of air that may be under positive pressure are life-saving measures. As immediate action is often necessary, there may not be time for fluoroscopic study or the making of a roentgenogram. A large pneumothorax may be recognized by the usual physical signs of pneumothorax. A small pneumothorax pocket, limited by pleural adhesions, usually cannot be localized by physical signs but, if near the mediastinum and under high positive pressure, may be as rapidly fatal as a large pneumothorax of lower pressure. If a small pneumothorax which cannot be localized is assumed to be present, an aspiration needle should be introduced into the pleural cavity in various places near the site of the torn pleura until the pneumothorax pocket is found.

All operations involving the pleural cavity and some extrapleural operations on patients whose pleural cavities are not obliterated by adhesions result in traumatic pleuritis and formation of varying amounts of pleural fluid, with resulting increase in intrapleural pressure. An intrapleural pressure, therefore, that may be satisfactorily low immediately after, or a day or two after, operation will rise as pleural fluid forms and may require reduction by aspiration of fluid or of fluid and air on one or more occasions. A similar situation occurs if a postoperative hemorrhage takes place in the pleural cavity after, for example, removal of a mediastinal tumor, although the bed of the tumor may have been entirely dry at the time the thoracic wall was closed.

The lungs of patients who have undergone open intrapleural operations and who do not require a postoperative therapeutic pneumothorax should be expanded as quickly as possible either by the inflation of the lung by positive pressure in the gas anesthesia apparatus before the incision in the parietal pleura has been closed air tight or by postoperative aspiration by needle of all the air remaining in the pleural cavity at the end of the operation. The evacuation of all pneumothorax air has the twofold advantage of preventing postoperative emphysema of the thoracic wall and of causing adhesion between the visceral and parietal pleurae which adhesion tends to prevent or limit an empyema.

that might occur if the pleura were infected. When an entire lung has been removed and the thoracic wall closed without damage of the pleural cavity, the size of the pneumothorax should be regulated with the aid of the fluoroscope and by withdrawal or introduction of air so that the mediastinum is kept in its normal position. When infection of the pleural cavity does not occur, a sterile exudate gradually fills the pleural cavity and eventually becomes organized. During the period of formation of the exudate, air or air and fluid may need to be aspirated from time to time in order to keep the mediastinum in its normal position.

The accumulation of wound serum after pericardiectomy may cause fatal cardiac tamponade. As there is danger of injury to the heart from needling of the space between the pectoralis major muscle and the bare heart in order to find a fluid pocket, provision for drainage of fluid away from the heart should be made at the time of operation, either by deliberate opening of the mediastinal pleura next to the heart or, if the pleural cavity is obliterated by adhesions, by manual tunneling between the pectoralis major muscle and the thoracic wall from the site of the opening in the thoracic wall to the axilla. Incidentally, with regard to the postoperative care of pericardiectomized patients, prompt venesection with removal of 500 cc or more of blood may be valuable if an atrophied myocardium gives signs of being unable to function properly after the sudden removal of the thickened pericardium that has been constricting it.

Air-Tight Tube Drainage of Pleural Cavity—Drainage of the pleural cavity after lobectomy or pneumonectomy for infectious pulmonary conditions and after certain other interpleural operations calling for drainage requires careful control of the intrapleural pressure by adjustment of some type of apparatus attached to a water-seal bottle. A very negative intrapleural pressure should be avoided during the first postoperative days because of the circulatory impairment that may result from sudden traction on the mediastinum. A pressure of -8 or -10 cm of water is safe during the first day or two, and may then be gradually lowered to -20 or even -30 cm of water if advisable. Cardiorespiratory disturbance, pain or pleural bleeding suggests that the pressure is too low.

In drained pneumonectomized patients the intrapleural pressure should be so regulated that the mediastinum is kept at first approximately in its normal position, and later gradually drawn into the empty pleural cavity so as to help to obliterate it. In drained lobectomized patients the remaining lobe should be expanded as quickly as is safe so that it will fill the space formerly occupied by the lobe that was removed and by adhesion of the expanding lobe to the parietal pleura reduce the extent of pleural surface susceptible to infection. Furthermore, the expansion and adhesion of the remaining lobe tend to seal

off the stump of the bronchus of the resected lobe, thereby reducing the chance of formation of the bronchopleural fistula

Cessation of fluctuation of fluid in the tube near the water-seal bottle may be caused by a very low pressure, by occlusion of the tube by exudate within it or by the covering of the inner end of the tube by an expanding lung or a rising diaphragm. The tube should be kept patent in cases of lobectomy until the interpleural space is obliterated. Unless absolutely necessary the tube should not be removed for inspection until at least seven days after operation, because the lobe that has been caused to expand by the negative intrapleural pressure probably does not become sufficiently firmly adherent to the parietal pleura before then to prevent partial or complete collapse of the lobe when air at atmospheric pressure is admitted to the pleural cavity on removal of the tube. The same principle is applicable to cases of simple empyema. Empyema drainage tubes of the proper large size and properly placed do not need removal for replacement or cleansing oftener than every one or two weeks. On these occasions the decrease in size of the empyema cavity should be determined by measurements, and the length of the tube should be checked so as to make certain that its inner end lies in the cavity, just beyond the parietal pleura.

Evacuation of Pulmonary Secretions—The importance of this subject is stressed by being considered under both "Preparation for Operation" and "Postoperative Management," and the dangers of stasis of secretions have been mentioned in various parts of this article.

Many measures are available to promote efficient evacuation of secretions. If secretions are present in the pharynx during, or at the end of, the operation, they should be aspirated by the anesthetist. As soon as the patient awakens from anesthesia and while the table is still in the Trendelenburg position, the patient should be directed to cough until he expectorates all movable secretions. Until the patient is fully awake and able to cough efficiently, and perhaps during sleep the first day or two after operation, his bed should be kept in the Trendelenburg position (10 to 15 degrees) to promote gravitation of secretions toward the mouth. Patients who are able to expectorate more efficiently when lying flat or sitting up should be allowed to assume the optimum position if their general condition permits. In some patients expectoration is facilitated by posture on one or the other side, but no patient should sleep with the side of the secreting lesions uppermost, because of the danger that infectious secretions will gravitate to the dependent, uninfected lung.

Heavy doses of narcotics should not be given, since they interfere with voluntary coughing and, therefore, promote stasis of secretions. Heavy doses of opiates are likewise dangerous, as they obtund the cough.

reflex. Doses of opiates just sufficient to allay pain are valuable in that efficient coughing is thereby favored.

A few deep breaths followed by coughing are a simple and often effective means of evacuating sputum. The procedure should be directed by a nurse or a surgeon at regular intervals, the duration of which should depend on the amount of sputum to be evacuated. Patients unwilling to take deep breaths may be got to do so by inhalation of 10 or 15 per cent carbon dioxide in oxygen. During coughing, the area of the thoracic wall that has been weakened by the resection of a rib or ribs should be supported by the hand of a nurse or a surgeon. Secretions that are too viscid to be expectorated may be loosened by steam inhalations, by hot drinks and by such expectorants as ipecac, iodides and ammonium chloride.

In spite of a trial of the various measures suggested, some patients are unable to evacuate their pulmonary secretions, which, if long retained, may lead to serious complications. Aspiration, perhaps at intervals of two hours or more, by intranasal introduction of a catheter into the trachea and bronchi according to the method described by Haight,⁵ will prove invaluable in such cases. In occasional instances, if this method cannot be carried out effectively, the bronchoscope should be used for aspiration of secretions and the shrinkage of swollen mucous membrane by direct medication with gauze applicators.

Pain—Severe pain after most thoracic operations, even those requiring very long incisions, is rare if the surgeon has been gentle while operating and if gentle retraction of tissues has been possible. Small doses of opiates should keep the patient reasonably comfortable. If the pain should be greater than the surgeon expects, the dressing may be found to be too tight or too loose. The incision should be inspected in order to determine whether any stitches are too tight, whether the dressing is adherent to the incision and whether there is an accumulation of fluid in the wound under pressure. If a wound has been packed, undue pain may be caused by too tight packing. The placing of a large sheet of rubber dam between the packing and all exposed tissues at the time of operation and at successive dressings is one of the most important means at the surgeon's command to reduce the amount of postoperative pain.

Since muscle spasm is a frequent cause of postoperative pain, changes in the patient's posture may prove useful. If an incision has been made in the region of the shoulder girdle, the shoulder of the side operated on should not be touched in moving the patient. He should be turned on his side by traction on the hip and should be caused to sit up by being lifted by a hand placed behind the neck. The pain due to spasm

⁵ Haight, C. Intratracheal Suction in the Management of Postoperative Pulmonary Complications, *Ann Surg* 107 218-228, 1938.

of muscles incised in thoracoplasty and other parascapular incisions may be overcome by passive circular movements of the arm two or three times a day, beginning on the day following operation. Within three or four days passive movements may be succeeded by active movements. These early movements have the additional advantage of preventing late limitation of movements of the shoulder girdle. In some cases massage and heat are useful.

Abdominal Distention—Apart from the abdominal discomfort caused by this condition it may be an important cause of dyspnea in patients whose respiratory reserve is already low. It should be remembered that relief of the distention may prove to be an important means of relieving dyspnea. Acute dilatation of the stomach has been reported a number of times after thoracic operations, its prompt recognition and treatment are life saving.

Emphysema of the Thoracic Wall—When any amount of air is left in the pleural cavity after an operation in which the parietal pleura has been opened, coughing is likely to drive some or rarely, all the air out of the pleural cavity into the tissues of the thoracic wall. When large amounts of air enter the thoracic wall, the air usually moves to the neck, the head, the arms and the lower part of the trunk. Only small amounts of air enter the mediastinum from the base of the neck. Great pressure on the mediastinal organs from mediastinal emphysema with resulting dysphagia and cardiorespiratory decompensation usually occurs only when air in the pleural cavity is driven directly into the mediastinum through a tear or an incision in the mediastinal pleura or, indirectly from the lung, when communication has been made traumatically or surgically between a bronchus and the pulmonary parenchyma.

Emphysema of the thoracic wall, head, neck and trunk is uncomfortable but not dangerous unless the distention is so great that circulation and respiration are interfered with. In this event, short decompressing incisions should be made in the skin and perhaps through the fascia covering the muscles. Mediastinal emphysema of dangerous extent should be decompressed by continuous cup suction over an incision through the skin and cervical fascia in the suprasternal notch.

The simplest means of preventing great degrees of emphysema in the presence of a pneumothorax are air-tight suture of incisions in the parietal pleura and the prevention of hard coughing after operations in which air-tight closure cannot be effected. If these means fail, progressive emphysema can be prevented by aspiration of all air remaining in the pleural cavity. In certain cases, however, maintenance of a pneumothorax is important, and the surgeon is then faced by the dilemma of choosing between loss of the pneumothorax and progressive emphysema, which, however, usually stops progressing in two or three days as a result of sealing by exudate of the gaps in the parietal pleura.

Ordinarily, the extent of emphysema is determined by the volume of the pneumothorax but if an should continue to enter the pneumothorax from a tear, from an incompletely closed incision in the lung, from a bronchopleural fistula or through an imperfectly closed incision in the thoracic wall, the emphysema may increase indefinitely. In such cases the amount and pressure of the pneumothorax must be reduced by frequent aspirations of air by needle or by continuous aspiration with an intercostal catheter if the source of the air entering the pleural cavity cannot be checked.

Wound Infection—Infection of large thoracic incisions in debilitated patients is very dangerous and may be fatal unless prompt treatment is instituted. Infection of a parascapular incision and of the great subscapular and axillary spaces that are continuous with the incision, such as may occur after a posterolateral thoracoplasty, is especially grave. An attempt to control such an infection by reopening of an inch or two of the incision and introduction of a drainage tube is likely to fail, because the tube will not drain the pus from parts of the subscapular and axillary spaces that tend to be shut off from the main incision by the apposition of tissues. In such cases the entire length of the incision should be reopened and the subscapular and axillary spaces packed with gauze in which catheters or Carrell-Dakin tubes are placed for intermittent instillation of antiseptic solution. Other infected incisions, in which the extracostal tissues have been extensively separated from the thoracic wall during the operation, should be similarly treated.

Infections that are apparently limited to the subcutaneous tissue should, of course, be treated by an opening of the infected part of the incision only to the muscle fascia. A collection of serum deep in an uninfected wound should be aspirated so as to prevent the serum from working through the incision to the skin, with resulting infection of the wound from organisms on the skin.

Miscellaneous Matters—Incisions in the skin of the back take longer to heal solidly than do those, for example, of the anterior surface of the abdomen. If the stitches are removed on the sixth or seventh day after operation, the incision should be supported by straps of flamed adhesive tape for at least three or four days.

Fluids and food can usually be given much sooner to patients on whom thoracic operations have been done than to those who have undergone abdominal operations. Patients with chronic thoracic disease, especially those who are to have a staged operation, should be given iron and, in some cases, blood transfusions for the anemia that is usually present.

Apart from purely surgical considerations, the time which patients should spend in bed after thoracic operations depends on considerations

imposed by their particular diseases. Tuberculous patients who have been treated by major surgical operation should not be permitted to get out of bed as soon as their wounds have become solidly healed and the symptoms of active tuberculosis have disappeared. Such patients should be kept in bed under a sanatorium type of regimen for at least six months after operation and then, if the tuberculosis is apparently entirely quiescent, should spend from six to twelve months gradually increasing their physical activities before returning to work. Such a plan for convalescence is important in gradually rebuilding the essential resistance to tuberculosis. The postoperative convalescence of non-tuberculous patients who have had long, disabling illnesses should be relatively prolonged, according to the needs of the individual patient for gradual rebuilding of cardiac and respiratory functional reserve and of muscles atrophied by long disuse.

CONCLUSION

Close attention to the many important details of preparation of the patient for thoracic operations and of postoperative care will be rewarded by excellent clinical results that cannot be produced by perfect operations alone.

PREOPERATIVE AND POSTOPERATIVE CARE OF PATIENTS WITH LESIONS OF HEART AND OF PERICARDIUM

CLAUDE S. BECK, M.D.

CLEVELAND

A discussion of the care of patients who are about to be carried through an operation on the heart should include a consideration of the heart beat or, more precisely, a consideration of restoration of the heart beat. I need scarcely state the reason for this inclusion, because every one knows that the coordinated contractions of the heart can be lost during or after an operation on this organ. If one considers restoration of the heart beat, one must consider also respiration and the oxygen required to sustain life, because all three of these are joined together to do one thing, namely, to supply oxygen to the cells. This is shown in the accompanying chart.

PRESERVATION OF VITAL PROCESSES

Oxygen, Respiration and Circulation—The distribution of oxygen cannot be interrupted longer than a few minutes without destruction of the respiratory center and other brain centers. It is known that the duration of this possible interruption is distressingly short if recovery is to take place. Data on duration with full recovery for human beings are scant. Weinberger, Gibbon and Gibbon¹ have shown that cats tolerated anoxemia for three minutes and ten seconds without neurologic disturbances. Permanent alterations were found if the period of anoxemia was longer than this. Perhaps it can be assumed that this period for human beings is about five minutes. A longer interruption leads to destruction of brain cells, adrenal glands and other structures. Among these delicate nerve cells or centers that die quickly from lack of oxygen is the respiratory center, although it is not always more destructible than other structures in the brain. Mollison^{1a} reported the case of a patient whose heart had stopped beating for not less than thirteen minutes with

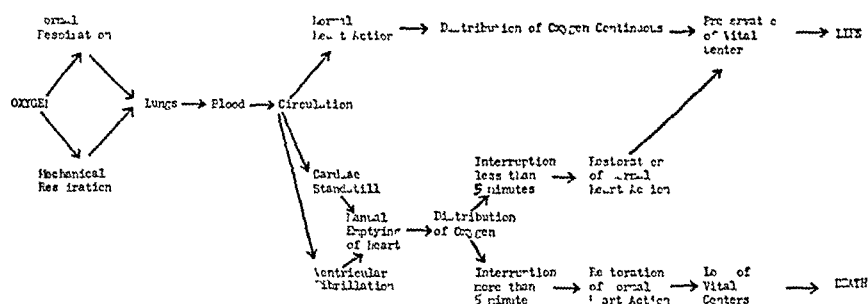
Aided by a grant from the Josiah Macy, Jr., Foundation

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1 Weinberger, L. M., Gibbon, M. H., and Gibbon, J. H., Jr. Temporary Arrest of the Circulation to the Central Nervous System. I. Physiologic Effects, *Arch Neurol & Psychiat* **43** 615-634 (April) 1940

1a Mollison, W. M. Heart Massage Through Abdominal Incision. *Brit J Child Dis* **14** 42, 1917

recovery of respiration. This patient subsequently was "more or less unconscious, though he could recognize his mother now and then. For ten days there was rigidity of the limbs, or choreic movements for thirty-six hours the screaming was almost continuous. For about twelve days he had incontinence. On September 15 [10 days after resuscitation] he became very violent, tore the bed-clothes, bit himself and spat. On September 22 he could sit up, he still had incontinence of urine. The nervous system seemed normal. He made eventually a perfect recovery and left the hospital on October 19." I have observed similar manifestations of cortical irritation in dogs after restoration of respiration and the heart beat. The one center that seems to determine success or failure is the center of respiration. The other brain centers seem to be of less importance. Restoration of the heart beat is almost always possible.



Mechanism of distribution of oxygen

RESUSCITATION

This discussion on resuscitation applies to experiences occurring in the operating room during induction of anesthesia, during operation or immediately after operation has been completed. If a breakdown in the oxygen system occurs when the patient is not in the operating room, there is little chance for success because of the time factor. The Drinker respirator and the Alvan Barach chamber are useful only in the presence of circulation. If the heart has stopped beating, there is no indication for any type of mechanical respiration by itself. Mechanical circulation must be added to mechanical respiration. The best mechanical device for respiration is one that can deliver air or oxygen into the lungs in a manner that resembles normal respiration as closely as possible. Also, it must be designed so that the surgeon can expose the heart to provide mechanical circulation.²

2 The need for mechanical respiration in the operating rooms of this institution does not occur frequently, but when it does the stake is high. The principle generally used consists of compression of the chest according to the method of

Restoration of the heart beat carries two requirements that must be met for success. The brain and especially the respiratory center must be kept alive, and the action of the heart must be restored. The latter without the former means failure. The chest is opened, the heart is exposed and the circulation is provided by emptying the heart by the hand. The circulation provided by hand is adequate to keep the brain alive.

Restoration of the heart beat without preservation of the respiratory center is readily feasible. Almost any normal heart that has not cooled can be made to beat. This does not apply to a heart that has been injured by disease. One of two conditions is encountered. One is standstill, the other is ventricular fibrillation. Different methods of restoration are necessary in these two conditions. The effective methods for restoration of action when the heart is in standstill consist of giving oxygen and epinephrine to the heart muscle. Oxygen is given by starting up the coronary circulation, which in turn is done by forcing blood from the heart into the pulmonary bed, aorta and coronary arteries by manual massage of the heart. It is needless to say

Schaefer and Sylvester. The anesthetist also has equipment to inflate the lungs with oxygen. These methods are not adequate. Unless respiratory function returns within a few minutes, the circulation usually ceases and death becomes total. Any one in the experimental laboratory working within the chest knows that aeration must be perfectly adjusted to maintain circulation. If it is not properly adjusted, the heart fails. The first time I used a mechanical respirator during operation on a human patient was about four years ago. The incident, perhaps the first of its kind, is sufficiently unusual to report. My patient had increased intracranial pressure from a meningioma arising from the tentorium. He was placed in the cerebellar position preparatory for operation, and when this was done his respiratory rate fell to 5 per minute. A ventricle of the brain was tapped, and when this was done the patient stopped breathing. He was placed in a Drinker respirator for one and one-half hours. Respiration did not return. The operation on the tumor could not be done with the patient in this respirator. An intratracheal tube was inserted. The respirator from the research laboratory was brought to the operating room and connected with the tube. It delivered air rhythmically and intermittently to the lungs. The patient was again placed in the cerebellar position, and the operation was begun. Three hours later the tumor was removed. As the wound was being closed, the patient began to breathe "on his own." He made an uneventful recovery. This respirator used compressed air and worked on the principle of the windshield wiper. Recently, Mautz has described a respirator for attachment to the commonly used closed system machines for administering anesthetic agents (Mautz, F. R. A Mechanical Respirator as an Adjunct to Closed System Anesthesia, *Proc Soc Exper Biol & Med* **42** 190-192, 1939, Resuscitation in the Operating Room, *Bull Am A Nurse Anesthetists* **8** 13-18, 1940). It will find a useful place in every operating room. For operations on the heart and for resuscitation in all types of operation, mechanical respiration through a face mask or through an intratracheal tube is essential.

3 In recent years, Gibbon, of Philadelphia, has carried out investigations along this line (Gibbon, I. H., Jr. The Maintenance of Life During Experimental

that a good supply of oxygen must be present in the lungs. Dilute epinephrine hydrochloride is injected into the blood through the right auricular wall. In the presence of ventricular fibrillation a different procedure must be used. Oxygen is essential, but epinephrine increases the irritability of the heart muscle and works against success. Procaine hydrochloride is necessary for success. This is injected into the blood through the right auricular wall and moved around to the coronary bed by massage. Procaine hydrochloride reduces tonus, and the muscle feels flabby after its use. It must not be used in excess. An electric current is then applied to the ventricles through large electrodes. The electric shock brings the muscle into a state of contraction. This is followed by a state of relaxation, and if conditions are proper the fibrillary movements will not return. Rhythmic, coordinated contraction is expected to appear after fibrillary movements have been destroyed. If the heart does not begin to contract at this stage, epinephrine hydrochloride or calcium chloride is used.⁴ These drugs increase the tonus of the heart. This increase in tonus can be readily felt by the hand. Soon rhythmic contraction will start. Not infrequently epinephrine is needed for a period of hours after the coordinated beat has returned. Epinephrine hydrochloride can be given intravenously as a drip with sodium chloride solution.

Defibrillation of the Human Ventricles with Restoration of Coordinated Beat—I am recording two experiences with human patients in whom fibrillation of the ventricles was made to cease and a coordinated beat was established. I believe these are the first such experiences with the human being to be recorded in the medical literature. Defibrillation of the dog's heart has been accomplished by Hooker⁵ and by Wiggers.⁶

REPORT OF CASES

CASE 1—E. J., a Negro boy aged 9 years, had sustained an injury to the knee. An operation was done to remove a fragment of bone from the knee joint on Dec. 7, 1938. The anesthetic was nitrogen monoxide and ether. The patient

Occlusion of the Pulmonary Artery Followed by Survival, Surg., Gynec. & Obst. **69**: 602-614, 1939). He has been able to preserve the brain in cats by injection of oxygenated blood under pressure into a branch of the aorta. In these experiments the blood was oxygenated outside the body in an atmosphere of oxygen.

4 Beck, C. S., and Mautz, F. R. The Control of the Heart Beat by the Surgeon, with Special Reference to Ventricular Fibrillation Occurring During Operation, Ann. Surg. **106**: 525-537, 1937.

5 Hooker, D. R. On Recovery of the Heart in Electric Shock, Am. J. Physiol. **91**: 305-328, 1929. Hooker, D. R., Kouwenhoven, W. B., and Langworthy, O. R. The Effect of Alternating Electrical Currents on the Heart, *ibid.* **105**: 246-249, 1933.

6 Wiggers, C. J. Cardiac Massage Followed by Countershock in Revival of Mammalian Ventricles from Fibrillation Due to Coronary Occlusion, Am. J. Physiol. **116**: 161, 1936.

was kept in a light zone of anesthesia throughout. At 9 15 the skin was being sutured, and the operation was practically completed. The respiratory rate was 19 per minute. At 9 20 the pulse suddenly became weak. Two minutes later it was impossible to get the blood pressure, and the respiratory rate was 4 per minute. At 9 25 the pulse could not be felt. The pulse disappeared before respiration stopped. An intratracheal tube was inserted after respiration ceased, and mechanical respiration was given by the respirator. I came on the scene at about 9 32. Dr. J. A. Clark, the surgeon, stated that the pulse had been absent for about 8 or 9 minutes. This agrees with the time given by the anesthetist. The preparation of the field was done by Dr. Clark while I put on gloves and a gown. It required a few seconds to open the chest. The heart was massaged several times with the pericardium intact. The pericardium was then opened, and the heart was observed. The ventricles showed a coarse, slow type of fibrillation. The heart was dilated, but time was not taken to determine the degree of dilatation. Rhythmic compression and relaxation of the heart by hand was done for about twenty minutes. This mechanical circulation produced a palpable pulse over the temporal artery. Never did the wink reflex return. The pupils were dilated and failed to react. Heat was applied to the body. Five cubic centimeters of 2 per cent procaine hydrochloride was injected into the cavity of the right auricle. The circulation was kept up by the hand. Large electrodes were placed on the ventricle, and a shock of about 1.5 amperes was sent through the heart. Three shocks were used. They produced forceful jerks of the body. The fibrillation stopped after these shocks. The heart was in standstill. The heart muscle was flabby in the hand and was without normal tonus. Epinephrine hydrochloride was injected into the blood through the right auricle, and massage was continued. The heart remained flabby. Five cubic centimeters of 1 per cent solution of calcium chloride was injected. The heart remained flabby. It was then noted that the lungs were not properly inflated and that the tube was not in the trachea. It is probable that it slipped out when the patient jerked with the application of the electrical shock. The tube was inserted in the trachea, and the lungs were properly expanded. The interval between the shocks and the discovery that the tube was out of the trachea was about ten minutes. There were a few moments of good aeration, and then the heart started up in a forceful rhythmic contraction of 70 per minute. This occurred at 10 12, forty-seven minutes after the pulse disappeared. The radial pulse was easily palpable. The heart was observed for twenty minutes, and the incision in the chest was closed. The pulse later became weaker. There was no reflex at any time. The pulse disappeared at 12 00 o'clock. Necropsy showed no anatomic cause of death.

Comment—The experience with this patient is noteworthy in several respects. Ventricular fibrillation was destroyed, and a normal heart beat was obtained. Inasmuch as this was accomplished on the human being, it may have some historical interest. It emphasizes the viability of the heart muscle. The heart beat had been absent forty-seven minutes. It also indicates the need of oxygen before the heart will start to beat. Ultimate success without respiration is not possible.

CASE 2—F. B., a Negro boy 13 years old, had ptosis of the right eyelid following an injury. Transplant of fascia lata for correction of the ptosis was carried out on July 27, 1939. The anesthetic was nitrogen monoxide and ether. As the last silk suture completing the operation was about to be placed the operator

was informed by the anesthetist that respiration was not normal. At 9 22 respiration had ceased, the pulse rate was 30 per minute. At 9 26 the pulse could not be obtained. An airway was inserted into the pharynx. Epinephrine hydrochloride was injected into the heart. The patient was placed in a Drinker respirator, but it was impossible to expose the heart and provide circulation with the patient in this respirator. He was taken out and given mechanical respiration by means of the Mautz respirator. At 10 05 the heart was exposed by Dr John Thornton, who at 10 09 began to move the blood by hand. The tone of the heart improved, and for forty-five seconds he obtained what he thought were weak coordinated contractions. These were replaced by fibrillary movements. Dr Thornton sent a current through the heart, but it did not stop the fibrillation. At approximately 10 45 I was asked whether I would like to try to defibrillate the ventricles of the heart. I found coarse fibrillary movements of the ventricles, it was obvious to any one that the ventricles were fibrillating. The manual emptying of the heart expelled sufficient blood to produce a palpable temporal pulse. About 2 cc of 2 per cent procaine hydrochloride was injected into the blood through the right auricle. The heart was flabby. An electrical shock was sent through the heart about five times. This did not destroy the fibrillary movements. The heart was very flabby but of good color. Solution of calcium chloride was given through the right auricle. This improved the tone, but fibrillation continued. I desired to increase tone and irritability, and, contrary to past experience, I gave some epinephrine. This increased the tone, and I could feel the heart squirming in my hand. After a few moments the heart was beating. Fibrillation had dropped out and was replaced by a coordinated contraction at 11 05. Epinephrine hydrochloride was given in an intravenous drip. The incision was closed. An electrocardiogram showed auricular fibrillation, right bundle branch block and right axis deviation. The radial pulse was felt easily. There were no reflex responses. Mechanical respiration was carried out throughout. The pulse continued until 3 00 o'clock, when it disappeared.

Comment—In this patient the nervous system was dead for a long time before the action of the heart was restored. It is interesting that a coordinated ventricular beat was obtained ninety-nine minutes after the heart had stopped beating. It is also interesting that the fibrillary movements of the ventricle ceased and a coordinated contraction began after administration of calcium chloride and epinephrine hydrochloride and that the electric shock was not needed to stop the fibrillary movements. In work with the dog's heart both Wiggers and I have found that epinephrine works against success when the ventricles are fibrillating. It is valuable when the ventricles are in standstill. Perhaps the previous use of procaine hydrochloride makes some difference in the effect obtained by epinephrine.

Establishment of a Resuscitation Squad—The demands for successful resuscitation are such that a program of action must be in existence before the emergency arises. It is well to have a resuscitation squad in every hospital so that the proper steps can be taken immediately and without deliberation. The procedure is divided into two stages. The

first stage concerns preservation of the respiratory center and the other centers in the brain. As soon as respiration ceases or as soon as the heart stops, oxygen must be introduced into the lungs by mechanical respiration, hence the need for a satisfactory breathing machine. It must also be moved from the lungs to the brain by artificial respiration. This involves exposure of the heart and manual massage. When the emergency occurs, the anesthetist gets oxygen into the lungs, and the surgeon exposes the heart and takes care of the circulation. This must be done probably within five minutes for recovery. The second stage is not an emergency. Time can be taken to call some one who knows how to restore the heart beat. The heart can be made to beat if the proper steps are taken. These steps can be learned in the experimental laboratory.

CARE OF PATIENTS WITH ACUTE COMPRESSION OF THE HEART

Acute compression of the heart occurs in the presence of purulent pericarditis, stab wounds of the heart, gunshot wounds of the heart, rupture of the heart following contusions, rupture following softening of the myocardial wall from disease processes, rupture of the base of the aorta, rapidly forming exudates and transudates and intrapericardial hemorrhage associated with the hemorrhagic diatheses. It may also occur after operations on the heart and after other operations in the mediastinum, such as removal of a mediastinal goiter. It may occur in patients with mediastinal infections, especially those which produce gas, and also in patients with pressure pneumothorax. Each of these conditions kills the patient when the compression on the right auricle or the venae cavae exceeds the pressure inside these channels. The truth of this statement is obvious, because the walls of these channels yield to pressures within and without. Normally the pressure in these vascular channels is less than the pressure of the atmosphere, but when they are compressed by outside forces the pressure inside rises to about 15 or 20 cm. of water. Venous pressure cannot rise much higher than this, and a compression force of 15 or 20 cm. can be considered as the fatal level. The circulation can be restored by reducing the compression force or by raising the venous pressure. Either or both of these factors can be used in treatment.

Purulent Pericarditis—The patient's life is threatened because of two factors. One is infection, the other is compression of the heart. Usually the patient is critically ill, and the need for relief is urgent. Relief can be given by raising the venous pressure. Venous pressure can be elevated by transfusion or by administration of dextrose or sodium chloride solution intravenously. This is done as a preoperative measure. My associates and I have demonstrated the effectiveness of

this experimentally. When the diagnostic tap of the pericardium is made, it is well to remove as much of the pus as possible. If the pus is not too thick to come away, the compression can be reduced in this way. With patients who are critically ill from purulent pericarditis it is advisable not to use large doses of sedative drugs that will depress respiration before the operation is carried out. The use of procaine hydrochloride combined with light nitrogen monoxide anesthesia is to be preferred.

After operation an oxygen tent is almost always beneficial. The patient is usually most comfortable in Fowler's position, but he should be encouraged to lie on either side to improve drainage from the pericardial cavity. It is not advisable to keep a catheter in the wound, because over a long period it can produce erosion of an auricle or a ventricle. Irrigation with physiologic solution of sodium chloride is advisable. The use of antiseptic solutions is not without danger. I have shown that dilute solution of sodium hypochlorite U. S. P. (Dakin's solution) can produce chronic cardiac compression because of the formation of scar tissue.⁷ Scrupulous aseptic technic is indicated to prevent contamination with other organisms. Sulfanilamide should be used only for those infections that respond to the drug. The current literature warns against indiscriminate use of this drug.

Stab Wounds and Gunshot Wounds of the Heart—In these injuries the patient's life is threatened by compression of the heart due to accumulation of blood in the pericardial cavity and by the injury to the heart itself. Either may be fatal. In the majority of cases the cause of death is compression rather than intrinsic damage to the heart.

The treatment of these injuries concerns primarily the removal of blood from the pericardial cavity. It also concerns the removal of a foreign body if one is present. While the operating room is being made ready, it is advisable in selected cases to prepare a donor for transfusion or to take blood from a bank and give it. If the circulation is almost gone, solutions of acacia, dextrose or sodium chloride can be given. External heat should be applied. As a rule the body becomes cool when the circulation is seriously impaired. Sedative drugs may or may not be necessary. Sometimes the operation is undertaken without anesthesia because the patient is almost unconscious and the respiratory exchange is so reduced that sufficient anesthetic cannot be introduced into the lungs and the blood.

Sometimes a dry wound of the heart is produced. This is possible if the knife blade penetrates the ventricle obliquely or if it does not enter the cavity of the ventricle. These wounds are usually not recognized as

⁷ Beck, C. S. The Effect of Surgical Solution of Chlorinated Soda (Dakin's Solution) in the Pericardial Cavity, *Arch. Surg.* **18** 1659-1671 (April) 1929.

being deep enough to reach the cavity of the heart, and as a rule they heal without complication. They may be complicated by infection and delayed hemorrhage. In other instances the amount of blood shed into the pericardium does not produce serious compression of the heart. If infection does not supervene, the blood is absorbed without leaving adhesions and the wound heals without complication.

The postoperative care involves restoration of blood, administration of oxygen and rest. The blood volume should be brought back to normal. As a rule, an oxygen tent is beneficial. If there is any blood in either pleural space, it should be removed. The patient should be kept quiet, so that the intracardiac pressure will not be elevated and produce additional tension of the sutures. Morphine can be used. Infection is the most common and serious complication. If it develops, drainage of the pericardial cavity is necessary. If empyema develops it must be treated. The patient should be kept in bed until the wound is firmly healed.

CHRONIC CARDIAC COMPRESSION

This condition is produced by a variety of lesions, the most common of which are the compression scars referred to by most authors as constrictive pericarditis or as Pick's disease. Tuberculous exudate, pus containing the usual pyogenic bacteria, noninfected transudates, exudates and blood can produce chronic compression. Tumors can compress the heart. In a case reported by Crynes and Hunter⁸ the heart was herniated and strangulated through a rent in the parietal pericardium. In all these conditions the venous pressure must be maintained at a high level. It must be higher than the compression force on the heart. Blood letting in these conditions is contraindicated. As a preoperative measure as much of the fluid as possible is removed from the abdomen and chest. This is done by tapping the chest and abdomen and by using diuretics. The removal of fluid by tapping must be done carefully, because as the pressure on the viscera is released the venous pressure has a tendency to fall, and as it falls the filling of the heart is reduced. The patient may faint and become pulseless. A tight abdominal binder is useful when this happens. Not infrequently the protein content of the blood is reduced in the presence of chronic compression. A diet high in protein and vitamins may be used to correct this deficiency. Respirations should not be depressed by use of strong sedatives.

⁸ Crynes, S. F., and Hunter, W. C. Traumatic Rupture of the Pericardium. Study of Twenty-Two Cases with Two and One-Half Year Period of Survival in One Case, Review of Literature, *Arch Int Med* 64:719-746 (Oct) 1939. Hunter, W. C., and Crynes, S. F. Traumatic Rupture of the Pericardium, *Mod Concepts Cardiovasc Dis*, February 1940, vol 9, no 2.

After operation for chronic compression an oxygen tent is highly beneficial, especially for the first three to five days. Morphine is used as indicated. Food is given on the evening of the operation if the patient is not nauseated. Food high in protein is given early. Infusions are contraindicated. Fluids by mouth are given as requested by the patient. There is sufficient fluid in the body tissue so that administration of fluid is not urged. The patient breathes more easily in a "semi-Fowler" position. The position is changed frequently, so that the patient lies on either side. In the presence of noninfected lesions drainage of the pericardial cavity or mediastinum to the outside is always contraindicated. In the presence of compression scars I open the left pleural cavity so that the pericardium or mediastinum drains into the pleural cavity. As a rule a few hundred cubic centimeters of fluid collects in the pleural cavity by the second or third day. It is advisable to remove this fluid by tapping the chest with a needle. In patients with chronic purulent pericarditis the drainage is to the outside as with acute lesions. Chronically infected, thick-walled cavities have a tendency not to heal. In such cases strong suction as advocated by Neville⁹ can be tried.

In my series of cases of chronic compression due to scars it has been noted repeatedly that the circulation improves at the time of operation when the scar is removed and that some of this improvement is lost subsequently. I interpret this as due to dilatation of the heart and weakening of its beat. One of my patients died eight hours after operation. He had the highest venous pressure observed in my series (42 to 45 cm). He also probably had the highest degree of compression in the series. The scar was removed without complication. The circulation improved while he was on the operating table. The heart dilated because it was filled from distended veins. At the same time the sustaining scar had been removed. The degree of dilatation could have been reduced by blood letting. It is to be held in mind that blood letting may be indicated *after* the removal of compression scars. This is not necessary as a routine. I have not done it in other patients, but I believe it might be beneficial in patients with a high degree of compression.

A consideration of some importance that I have brought out in a study of this subject both clinically and experimentally is the development of atrophy from disuse of the heart muscle after it has been compressed for a time. The heart becomes smaller when compressed. The size of the organ as a whole is diminished, and Dr. J. T. Roberts and I have shown that the individual muscle fibers become smaller than normal. Atrophy of disuse accounts for the prolonged recovery period not infrequently seen after operation. In some patients it takes six months

9 Neville, J. V. H. The Treatment of Chronic Empyema by Continuous High Vacuum Suction, *Surg., Gynec. & Obst.* 69: 240-246, 1939.

or longer for the edema and ascites to disappear and for normal strength to be recovered. In other patients the ascites disappears in a few weeks.

GRAFTS FOR REVASCULARIZATION OF THE MYOCARDIUM

This operation is still in the experimental stage of its development and therefore calls for little discussion concerning the care of patients. One must determine how much revascularization has been produced by the operation in patients on whom it has been performed. If the amount of revascularization is sufficient to establish this operation as a therapeutic procedure, a number of surgical problems will need a solution. One must view with caution the various contributions in this field of endeavor, and one must be as accurate in making conclusions as it is possible to be before applying any procedure to the heart for purposes of improving the circulation. Recently Thompson¹⁰ placed talc in the pericardial cavity of dogs and fourteen to twenty-one days later ligated both the right and the left coronary arteries near the aorta. To quote the author, "there was no longer any appreciable circulation of blood to the heart muscle through the normal channels, but the entire circulation was coming from the pericardium." Thompson applied the procedure to 10 patients with coronary disease, and 7 received "very marked benefit." Stanton, working in my laboratory, repeated Thompson's experiments. He was unable to demonstrate any beneficial effects from the use of talc. The mortality following ligation of the descending ramus of the left coronary artery was the same in a series in which talc had been used as in a series of normal control experiments. On the basis of our experiments my associates and I would not advocate this procedure.

OTHER OPERATIONS

These include the Brauer operation of cardiolysis, decompression of the heart for cardiac hypertrophy, resection of nerves for angina pectoris and ligation of the "uncomplicated" patent ductus arteriosus. I shall not attempt to discuss the preoperative and postoperative care in these conditions. The achievements of Gross¹¹ have placed the patent ductus arteriosus in the field of surgical treatment. Now that success has been demonstrated, the operation to ligate the communication should be carried out.

10 Thompson, S. A. Development of Cardio-Pericardial Adhesions Following the Use of Talc, *Proc Soc Exper Biol & Med* **40** 260-261, 1939, An Operation for the Relief of Coronary Artery Disease. A Preliminary Report, *Quart Bull, Sea View Hosp* **5** 175-182, 1940.

11 Gross, R. E. A Surgical Approach for Ligation of a Patent Ductus Arteriosus, *New England J Med* **220** 510-514, 1939, Surgical Management of the Patent Ductus Arteriosus, with Summary of Four Surgically Treated Cases, *Ann Surg* **110** 321-351, 1939.

ELECTROCARDIOGRAPHIC OBSERVATIONS IN SURGICAL
TREATMENT OF THE HEART

These observations were made by Feil and Rossman¹² The following abnormalities were found during operation ventricular extrasystoles, ventricular tachycardia, deviation of the ST segment, auricular flutter, arteriovenous nodal rhythm with retrograde conduction, arteriovenous nodal tachycardia, intraventricular block, transient ventricular fibrillation, wandering pacemaker, changes in direction of the T wave, auricular extrasystoles and electrical alternans From the practical point of view it is desirable to know what can be done to prevent or reduce these responses and how to correct them after they appear On the basis of experiments from this laboratory, Mautz¹³ concluded that quinidine sulfate U S P given systemically lessens the danger of auricular or ventricular fibrillation and that procaine hydrochloride applied to the surface of the heart reduces the irritability of the organ to external stimuli, such as those accompanying operation Recently Wiggers and Wegria¹⁴ have found these drugs effective in cases of ventricular fibrillation It has been the practice to give 0.2 Gm of quinidine sulfate the night before operation and two doses of 0.4 Gm each the morning of operation While the amount of drug did not prevent disturbances of rhythm in the patients observed by my associates and me, it was concluded by Dr Feil that the frequency of these disturbances was reduced after administration of the drug Two cubic centimeters of 5 per cent procaine hydrochloride was applied to the surface of the heart in some of our operations Experimentally this drug not only reduces the irritability of the heart to external stimuli but reduces the rate of the heart beat When injected into the blood stream it makes it uniformly possible to defibrillate the ventricles by the use of an electric shock, and it also makes the ventricles less susceptible to development of fibrillation Our use of this drug on the human heart has been somewhat restricted, because the drug in large doses makes the heart muscle flabby and reduces the tone of the muscle

In several of our patients auricular fibrillation or auricular flutter developed during the postoperative period These complications appeared

12 Feil, H, and Rossman, P L Electrocardiographic Observations in Cardiac Surgery, *Ann Int Med* **13** 402-414, 1939, Electrocardiographic Observations in Cardiac Surgery, *Mod Concepts Cardiovasc Dis*, January 1940, vol 9, no 1

13 Mautz, F R Reduction of Cardiac Irritability by the Epicardial and Systemic Administration of Drugs as a Protection in Cardiac Surgery, *J Thoracic Surg* **5** 612-628, 1936

14 Wiggers, C J, and Wegria, R Attempts at Quantitative Measurements of Fibrillating Thresholds for Mammalian Ventricles, *Am J Physiol*, to be published

suddenly The pulse became very rapid, and the patient became weak To these patients a digitalis preparation (digalen) was given intravenously It was injected through a hypodermic needle into a vein in doses of 1 minim (0.06 cc) per pound of body weight according to the method advocated by Pardee¹⁵ Thus a man weighing 150 pounds (68 Kg) should receive 15 cc of the drug If in thirty minutes the ventricular rate does not come down to the desired level, additional injections of 2 cc each can be given until the rate is normal It is to be borne in mind that the usual rate for a patient with fever is more rapid than for an afebrile patient, in the presence of fever the desired rate may be 110 per minute rather than 80 If the patient has ventricular tachycardia after operation, quinidine sulfate should be given by mouth It is interesting that in none of our cases did ventricular tachycardia develop If auricular paroxysmal tachycardia develops, pressure over the carotid sinus is frequently effective in terminating the attack If this is not effective, acetylbetamethylcholine hydrochloride (mecholy1) may be given subcutaneously in doses of 20 to 25 mg Auricular paroxysmal tachycardia did not develop in any of our patients

¹⁵ Pardee, H E B Hypodermic Digitalis Preparations, J A M A 85 1359 (Aug 15) 1925

PREOPERATIVE AND POSTOPERATIVE MANAGEMENT IN GYNECOLOGY

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This contribution deals only with essentials in the care of women subjected to gynecologic operations, it would not be practical to include every complication encountered before and after such operations

PREOPERATIVE PROBLEMS

History—A carefully elicited history is essential. If physicians listen attentively to a patient's story, they may be saved embarrassment, intelligent women literally direct the examiner to the site of their troubles. Symptoms of systemic diseases may be unearthed, these may prove of greater importance than the gynecologic problems.

If operations on the lower part of the abdomen or on the genitalia have been done previously, one should obtain a report not only of the indications for and the findings at those operations but of the procedures performed, the pathologic diagnosis of tissues removed, the character of the convalescence and the benefits which followed.

Examination—Every patient should be subjected to a complete physical examination to establish the state of her general health and to determine whether there are contraindications to surgical treatment. A clean specimen of urine should be examined, red and white blood cell counts should be made, together with an estimation of the concentration of hemoglobin, and blood should be drawn routinely for a Kahn test.

Most patients with myocardial damage can safely be subjected to major gynecologic procedures providing the heart is well compensated (Women with syphilitic aortitis and aortic insufficiency are poor surgical risks). It has been my privilege to be associated with a group who are intensely interested in cardiovascular diseases, they believe that patients with complicating cystocele, prolapse, large abdominal tumefactions (either uterine or ovarian) or bleeding fibroids which lead to notable anemia are best managed if these extra burdens are eradicated. Nephritic patients are dubious surgical risks.

Secondary anemia, the result of excessive uterine bleeding, is frequent. Anemic women are more likely to have postoperative complica-

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tions than are those who have normal blood counts. I use repeated transfusions of citrated blood and prefer not to operate until the red blood cell count is over 4,000,000 per cubic millimeter and the value for hemoglobin is at least 10 Gm. Restriction of diet and medical measures are helpful adjuncts, but improvement in the blood picture is slow, and, consequently, for very anemic women I am "transfusion conscious."

Diabetes, which can be controlled, is not a contraindication to surgical intervention. The internist should manage the diabetic patient's post-operative care.

A leukocyte count over 12,000 per cubic millimeter or a temperature above 99.5 F. demands careful investigation. Occasionally, fever and leukocytosis are caused by the genital pathologic condition. If, on the other hand, they result from an acute infection of the upper respiratory tract, elective operations should be postponed for two or three weeks, i. e., until the infection has subsided completely.

Elderly women may require abdominal operations for removal of ovarian tumors or carcinoma of the body of the uterus. In addition, one sees many women in the seventh and a few in the eighth decade of life with a large symptom-producing cystocele or with prolapse of the uterus. Age alone is not a contraindication to surgical correction of these lesions.

Patients with a profuse leukorrheal discharge are given douches with 1:20,000 mercury bichloride two or three times daily for several days before plastic operations and preferably for twenty-four hours before a laparotomy.

Preparation for operation includes thorough washing of the abdomen and vulva with soap and water and careful shaving of these areas. A cleansing tap water (not soapsuds) enema is given late in the afternoon of the day before operation. A high carbohydrate liquid diet is preferred for the evening meal before operation. A good night's sleep is assured by administration of a hypnotic, usually one of the barbiturates. Forty minutes before the anesthetic is to be started, a hypodermic injection of $\frac{1}{4}$ grain (0.015 Gm.) of morphine sulfate and $\frac{1}{100}$ grain (0.6 mg.) of atropine sulfate is given to patients on whom abdominal operations are to be performed, $\frac{1}{6}$ grain (0.01 Gm.) of morphine sulfate with the atropine sulfate is all that is usually needed before plastic operations.

I have been pleased with the preoperative hypnosis induced in selected patients by rectal administration of avertin in amylene hydrate. I have not considered it advisable to use this drug as a routine.

The usual anesthetic is ethylene, supplemented, if necessary, by a small amount of ether. Mercresin¹ is used to prepare the abdomen

¹ Mercresin tincture (Upjohn) contains 1 part of secondary amylmercuric iodide and 1 part of orthohydroxyphenylmercuric chloride in 1000 parts of a solvent containing 50 per cent alcohol and 10 per cent acetone.

vulva, vagina and cervix For abdominal operations it is necessary to prepare the vagina when one contemplates removing the entire uterus

OPERATION

A few comments about surgical technic may be appropriate Comfort of the patient, a low incidence of postoperative complications and lasting benefits from the gynecologic procedures are, in a large measure, dependent on a few essential principles, e g, masking of both the nose and the mouth by every one in the operating room, strict attention to asepsis, gentleness in handling tissues, complete hemostasis with avoidance of mass ligatures, abstinence from the use of plain catgut and employment of silk or the smallest caliber chromic sutures that are practical, use of rubber packs within the abdomen, avoidance of using gauze packs against small intestinal surfaces, and, finally, promptness in operating, with a minimum of trauma

I do not favor the routine use of stay sutures, they are unnecessary and may be harmful The promiscuous use of drains is ill advised Ventral hernias following gynecologic operations seem to occur in direct proportion to the use of abdominal drains and the presence of infections of the abdominal wall Consequently, when drains are used it is probably better to insert them through the vaginal vault or, if the cervix is present, through the cul-de-sac I have not found it necessary to drain routinely after total hysterectomies

ROUTINE POSTOPERATIVE CARE

Before considering the management of complications, I wish to outline my routine postoperative care, it has proved satisfactory

After both abdominal and vaginal operations the head of the bed is elevated 6 inches (15 cm) as soon as the patient has regained consciousness It is believed that this position tends to minimize pulmonary hypostasis and aids in elimination of feces and urine, also, if there is intra-abdominal infection it tends to aid localization in the most dependent portions, for example, in the pelvis, where the pus is accessible and can readily be evacuated

Ventilation with 5 per cent carbon dioxide and 95 per cent oxygen for one or two minutes on three or four occasions during the first sixteen hours after major operations seems to reduce the incidence of pulmonary complications, it also makes the patient more comfortable

I have abolished hypodermoclysis and proctoclysis in favor of intravenous administration of fluids After abdominal operations the patient is given 2,000 cc of 5 per cent dextrose in physiologic solution of sodium chloride immediately, six to eight hours being consumed in its administration After certain major vaginal procedures, 1,000 to

1,500 cc of fluid is advisable. As soon as nausea and vomiting have disappeared, fluids are allowed orally, water and tea are given first. Caution must be exercised so that the stomach does not become over-distended. In many instances, after abdominal section intravenous administration of 1,000 to 2,000 cc of fluid is desirable on the day after operation.

Solid food is allowed as soon as the patient desires it. In the absence of nausea, vomiting and distention the patient's wishes are permitted to determine what she eats and drinks.

For many years it has been my privilege to be associated with Dr. Arthur H. Curtis, chairman of the department of obstetrics and gynecology at the Northwestern University Medical School. From Dr. Curtis I learned a technic for managing the bladder which seems superior to other methods. Before I employed this technic 10 per cent of my patients had postoperative complications referable to the urinary tract. Today pyelitis and pyelonephritis have been eliminated from my postoperative worries, except in patients who have had previous renal infection or have sustained ureteral injury at the time of operation.

Patients are catheterized as often and as long as is necessary. I do not catheterize after a stipulated number of hours, the reasons for catheterization being (1) relief of discomfort in the lower part of the abdomen and (2) prevention of overdistention of the bladder.

Patients receiving intravenous fluid are catheterized when 1,500 cc has been administered, after administration of this amount of fluid there is usually about 300 cc of urine in the bladder. Others are catheterized earlier, i. e., as soon as they have distress referable to the bladder. My criterion of overdistention is the presence of more than 350 cc of urine in the bladder. One should beware of overflow from a distended bladder, this is characterized by frequent urination in small amounts.

Even after major operations, patients may be allowed out of bed, some succeed in urinating when permitted to use a commode. After most abdominal operations, spontaneous urination starts on the second or third day. After many plastic operations, particularly those which include correction of a cystourethrocele, the patient may be unable to urinate for a week or ten days.

It is impossible to catheterize a woman repeatedly without introducing bacteria into the bladder. However, cystitis occurs most often when the bladder has been traumatized, this permits bacteria to invade the mucosa. A frequent type of postoperative trauma to the bladder is overdistention, hence the care to prevent accumulation of more than 350 cc of urine. Residual urine, which remains after incomplete emptying of the bladder, is an important factor in the production of

inflammations of the urinary tract. Consequently, the second important step in the Curtis management is to prevent accumulation of residual urine. When a patient starts to void spontaneously, she is catheterized for residual urine. At first this must be done after each urination. Later, when the residual urine is less than 50 cc., she needs to be catheterized for residual urine only once or twice daily, this follow-up must be continued not only until the residual urine amounts to less than 15 cc. on two successive days but also until it is grossly clear.

Employing retention catheters after pelvic procedures tends to give the operator a false sense of security. The catheters are prone to become displaced or plugged by debris and may not empty the bladder completely. They should be irrigated frequently and the urine kept strongly acid if one expects to prevent obstructing deposits of urinary salts. After a retention catheter has been removed, it is vital that the patient be catheterized until the residual urine is grossly clear and is less than 15 cc. on two successive days.

If a patient has been catheterized once or twice after operation, I do not believe that the bladder is infected, and, in consequence, it is not necessary to check for residual urine. However, if she has been catheterized more than three times the bladder is potentially infected, and residual urine must be removed. Occasionally, despite such management, I encounter pyuria and cystitis. In recent years I have been gratified by the rapid improvement in infections of the lower part of the urinary tract following administration of sulfanilamide, e. g., 10 to 15 grains (0.65 to 0.97 Gm.) of the drug four times daily, together with an equal amount of sodium bicarbonate. In my experience, sulfanilamide is the most effective antiseptic for the urinary tract, unfortunately, some women do not tolerate it.

Relief from Pain—Comfort and quiet epitomize the ideal post-operative management of patients. During the first forty-eight hours after operation I employ hypodermic injections of morphine sulfate, $\frac{1}{6}$ or $\frac{1}{4}$ grain (0.01 or 0.015 Gm.), codeine sulfate, 1 or 2 grains (0.06 or 0.12 Gm.), pantopon (a mixture of hydrochlorides of opium alkaloids), $\frac{1}{3}$ grain (0.02 Gm.), or dilaudid hydrochloride, $\frac{1}{16}$ or $\frac{1}{32}$ grain (3.7 or 1.8 mg.), as often as is necessary for comfort. Nurses are warned to be sure that the bladder is empty before giving opiates to relieve pain in the lower part of the abdomen. After the third day one can usually control discomfort with acetylsalicylic acid. When food and fluids are taken readily, sleep is induced by hypnotics, e. g., phenobarbital, sodium amytal or pentobarbital sodium. For apprehensive patients I sometimes use 15 to 20 grains (0.9 to 1.2 Gm.) of chloral hydrate with 60 to 90 grains (3.88 to 5.82 Gm.) of sodium bromide given by rectal instillation. Not a few women obtain relief and relaxa-

tion from taking 1 drachm (4 cc) of elixir of phenobarbital three or four times daily during most of their stay in the hospital

Vomiting—It is to be expected that most patients will have nausea, with or without vomiting, for twelve to twenty hours after major operations. During this time fluids by mouth are forbidden. Occasionally a vomiting patient is given 8 to 10 ounces (240 to 300 cc) of warm soda water by mouth to promote spontaneous gastric lavage.

If vomiting continues after twenty-four hours or if distention of the upper part of the abdomen is recognized during the early postoperative days, there is no therapy which equals a Levine tube with continuous suction to keep the stomach empty. When continuous gastric suction is being employed, fluid balance and "blood chemistry balance" must be maintained by intravenous administration of fluids.

Bowel—Many patients are bothered by mild gas pains on the second, third and fourth days after abdominal operations. Within seventy-two hours after an abdominal operation decided relief from these pains is to be expected, a rectal tube aids in elimination of flatus. Employment of dry heat to the abdomen, preferably by means of a cradle for an hour three times daily, not only hastens wound healing and tends to make patients more comfortable but reduces the incidence and severity of postoperative gas pains.

When food and fluids are being enjoyed and retained, usually on the second or third day after operation, $\frac{1}{2}$ ounce (15 cc) of liquid petrolatum or of petrolagar is given night and morning. By the fourth evening, if there has been no bowel movement, 4 ounces (120 cc) of olive oil is administered as a rectal retention enema. On the morning of the fifth day, if there still has been no elimination, a warm tap water (not soapsuds) enema is given. Thereafter, if defecation does not occur in forty-eight hours, the rectal instillation of oil and the tap water enema, if necessary, are repeated.

Wounds—Abdominal Wounds. Laced corsets of adhesive tape are used routinely after abdominal operations. These corsets have many advantages over strips of adhesive tape. Since they are laced, the amount of tension on the dressings can be regulated, depending on the patient's comfort and the degree of abdominal distention. Also, the abdominal dressings can be changed as frequently as necessary without discomfort.

During the evening of the day of operation, the adhesive corsets are unlaced and most of the abdominal dressings are removed, a heat cradle is placed over the entire abdomen. This apparatus consists of a dome-shaped metal reflector equipped with several 60 watt bulbs so that dry heat may be applied to the abdomen. It is my desire in using these cradles to apply sufficient heat so that the patient is conscious of it.

but not enough to cause discomfort or perspiration. Abdominal heat cradles are used for about one hour three times a day throughout the stay in the hospital.

Abdominal cutaneous incisions are approximated with silver clips. These clips are loosened after forty-eight hours and removed after ninety-six hours, the abdominal incision is then splinted by many "butterfly" strips of adhesive tape which extend from one side of the abdomen to the other, across the incision. I do not believe that abdominal incisions become infected in the patient's room if the edges of the skin have been accurately approximated in the operating room, even though dressings are removed and the heat cradle is applied as early as eight hours after operation.

Adhesive corsets need to be removed and new ones applied at least once during the hospital stay. Patients wear these corsets for approximately three weeks after operation and remove them at home. At the end of that time, if the wound is perfectly healed, they are permitted to have tub baths, thereafter the bridges of adhesive tape across the incision loosen rapidly and are removed.

Special surgical garments are not recommended after routine abdominal operations. Patients are told that they may wear whatever is comfortable, whether it be a garter belt, a "two-way stretch," a corset or nothing.

Vaginal Wounds. After vaginal operations dry heat is applied to the vulva by means of lamps and reflectors. The heat is used three times daily for an hour if comfortable. If there is notable swelling or pain in the perineal wounds, hot wet dressings give relief.

After urination and defecation the vulva is irrigated with a weak potassium permanganate solution. Vaginal douches are not needed.

Silk sutures are removed from perineal wounds eight to twelve days after operation, nonabsorbable sutures are removed from the cervix sixteen to twenty days after amputation operations.

General Activity.—The patients' comfort is the chief indication for an increase in their activities. They are allowed to have the back rest elevated whenever they wish. They may be out of bed as soon as they desire, as a rule this is six or seven days after operation. More activity is encouraged nowadays than formerly. If a patient has an unexplained fever it is my practice to keep her in bed. If there has been a normal course, I encourage women to be out of bed early and to start walking as soon as they feel able.

With this routine most patients subjected to laparotomy, whether the operation is a replacement of the uterus or a total hysterectomy, leave the hospital in ten or twelve days.

Their activity at home is governed entirely by their general sense of well-being. They are told that they may be as active as they wish, so long as they stop and rest whenever they begin to be tired. I caution them that their convalescence will be easier if they avoid overfatigue, they will become normal more rapidly if they are not too ambitious and are willing to increase their activities gradually. Most patients return to their usual occupations about six weeks after major surgical procedures.

POSTOPERATIVE COMPLICATIONS

After major gynecologic operations one expects a moderate elevation of temperature, with the peak occurring on the second and third postoperative days. A rise above 101 F is not anticipated. My patients are usually afebrile by the fifth day.

Although the pulse rate frequently ranges between 100 and 120 for a few hours after operation, it should soon become stabilized. A marked disparity between the pulse rate and the temperature curve is as a rule of serious significance. I expect the pulse rate to follow or fall below the temperature curve. In the gynecologist's patients, postoperative tachycardia is usually caused by shock, dehydration, anemia or infection, digitalis is rarely indicated.

Vomiting should stop within eight to twenty hours after operation. A continuation of vomiting on the second and third days must be looked on with concern, a Levine tube should be passed.

Although most patients have some discomfort from gas pains, notable distention of the abdomen is not anticipated.

Pain during the first forty-eight hours can usually be controlled by an occasional hypodermic injection of morphine sulfate, codeine sulfate, pantopon (a mixture of hydrochlorides of opium alkaloids) or dilaudid hydrochloride. Consequently, severe pain that requires frequently repeated hypodermic injections or necessitates their continuation after the second day may be significant.

The unfavorable signs and symptoms which I encounter are undue rise of temperature, fever protracted beyond the fifth day, rapid pulse, continued vomiting, abdominal distention and severe or protracted pain.

The surgeon should be certain that his own house is in order before searching elsewhere for the explanation of a patient's failure to make a satisfactory convalescence. Most postoperative complications arise in the operative field or result from some abnormal situation at the site of operation.

Shock—I rarely see shock. It may occur on the operating table, as a result of undue intra-abdominal trauma or excessive loss of blood. The best treatment of shock is its avoidance, viz., by use of ethylene supplemented by ether as the anesthetic, by gentleness in manipulation.

of tissues, by accurate hemostasis and by avoidance of abdominal operations on markedly anemic patients and patients with active pelvic infections. During anesthesia the patient's pulse and blood pressure are recorded frequently, if the pulse becomes increasingly more rapid and the blood pressure falls, ephedrine may prove helpful. After the return from the operating room the usual measures for combating shock should be instituted, viz, application of external heat, elevation of the foot of the bed, intravenous administration of dextrose and transfusion of citrated blood, together with an adequate supply of oxygen often supplemented by ventilation with carbon dioxide and oxygen. In the presence of unexpected shock one must ascertain whether there is concealed hemorrhage.

Wounds—It is not uncommon to find tiny areas of softening in abdominal incisions after two, three or even four weeks. They are relatively painless and are blue, frequently they evacuate a few drops of bloody or oily fluid. This phenomenon seems to result from softening of the catgut in the subcutaneous fat, although annoying, it has no practical significance.

In the presence of sustained or unexplained fever the abdominal incision is searched for signs of infection, viz, redness, fulness, undue tenderness or fluctuation. When an infection of the abdominal wall is recognized, continuous hot wet dressings are applied, the margins of the skin are spread only if there is localized bulging with fluctuation. Promiscuous probing of abdominal wounds in a search for accumulations of pus is ill advised.

Bleeding from an abdominal wound six, eight or ten days after operation is said to be indicative of disruption of the abdominal wall. My experience with ruptured incisions is so limited that I cannot verify the significance of this symptom.

Infection in vaginal wounds, whether in the perineum, in the anterior vaginal wall or in the vault of the vagina, is to be expected when there are undue pain, fever and leukocytosis. Examination may reveal marked tenderness, induration, bulging and fluctuation at the site of the infection. It is my practice to apply hot wet dressings or to open areas of bulging and thus establish free drainage. The majority of these accumulations spread the suture lines and drain spontaneously.

Peritoneum—Peritoneal inflammation may be limited to the pelvis, or peritonitis may involve the entire abdominal cavity. If inflammation is limited to the pelvis the symptoms consist of pain and fever, the physical signs include distention of the lower part of the abdomen, tenderness and rigidity, together with marked pelvic tenderness, elicited on bimanual palpation. Treatment consists of administration of sulfamidamide in large doses, with forced fluids and sedatives as necessary for

relief of pain. A modified Fowler's position is desirable, and hot wet packs are used continuously over the lower part of the abdomen. Transfusions should be given if there is notable anemia. Usually fluids and food can be taken by mouth.

Generalized peritonitis is one of the more frequent causes of death after gynecologic operations. Its presence is to be suspected in a patient with high fever and a pulse which is rapid, thready and out of proportion to the febrile response, the leukocyte count may be high in favorable cases and low in patients with a poor prognosis, the tongue is dry, the facies is hippocratic, vomiting, abdominal distention and ileus are present. The management of peritonitis is discussed elsewhere in the symposium. My treatment includes continuous use of the Levine tube administration of fluids intravenously to maintain blood chemistry and fluid balance, free use of transfusions, intramuscular injection of azosulfamide (neoprontosil, disodium 4-sulfamidophenyl-2'-azo-5'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate) and sufficient morphine for rest. A rectal tube is desirable, but cathartics are not indicated, and frequent stimulating enemas should be avoided, they are exhausting.

Pelvic Cellular Tissues—Occasionally I observe fever following abdominal or extensive plastic operations when there is no obvious explanation for it. The patients may not be uncomfortable, although there is usually more pelvic tenderness than one anticipates after uncomplicated major surgical procedures. Some have brawny induration in the broad ligaments and paravaginal tissues, without fluctuation or subsequent drainage of pus. For this group, pelvic heat therapy is indicated, given either by diathermy or by the Elliott method.

In another group there is no palpable brawny thickening, and the inflammation seems to be restricted to the veins. The leukocyte count is usually low. One may be unable to substantiate a diagnosis of pelvic thrombophlebitis until there is extension of the process into femoral vessels or until pulmonary symptoms of embolism intervene.

Veins—I urge patients to move about early in their convalescence and encourage them to be out of bed by the fifth, sixth or seventh day. On the other hand, absolute rest in bed is desirable for a small group in whom thrombophlebitis is suspected. As a prophylactic measure against phlebitis large doses of thyroid may be given to women in whom postoperative phlebitis may be anticipated (chiefly because they are anemic, asthenic persons with marked varicosities in the lower extremities). I prescribe 5 grains (0.32 Gm.) of thyroid per day for several days before operation, the same amount is given after operation, as soon as food and fluids are tolerated.

Pulmonary embolism is the tragedy of pelvic surgery. This complication is observed in three forms, viz., small emboli with which there are

few physical findings, large emboli, with which there are classic pulmonary findings but from which the patients recover, and, finally, fatal emboli, with sudden death usually eight to twelve days after operation.

Femoral thrombophlebitis is one of the most annoying complications which I see. It usually attacks a patient with previously unexplained fever, putting in its appearance during the third postoperative week. It is said that femoral thrombophlebitis is rarely complicated by pulmonary embolism, whereas emboli usually arise from cryptic pelvic thrombophlebitis. During the past year I have been favorably impressed by the addition of high voltage roentgen therapy over the involved area to the usual methods of treating femoral thrombophlebitis, viz, rest in bed, elevation of the leg, application of cotton around the leg and employment of dry heat. Irradiation seems to shorten the course of the disease, the patients become afebrile within a week, swelling of the leg subsides rapidly, and pain also disappears promptly. I insist on rest in bed until there has been no fever for five days, and then activities are slowly increased as determined by the amount of edema when the leg is in a dependent position. I also advise use of an elastic stocking and expect it to be worn for at least six months.

Urinary Tract—A satisfactory method of managing the bladder has already been described, the value of sulfanilamide in eradicating infections of the bladder has been mentioned.

If there is vaginal drainage of urine, it may be due to a leak from the urethra, the bladder or a ureter. Many urinary fistulas close spontaneously. However, if they fail to heal after several weeks, one should determine their exact location and eventually correct them surgically. I am not impressed by plastic operations for the repair of ureteral fistulas, nephrectomy is usually necessary.

Gastrointestinal Tract—Vomiting that continues more than twenty-four hours after operation should be considered an indication for use of a Levine tube. This should be used continuously until the stomach empties normally. If one employs a Levine tube in this manner, marked distention of the stomach will be avoided.

Ileus after gynecologic operations usually results from peritonitis. Rarely is it of the adynamic type for which pitressin is helpful.

Intestinal obstruction is an infrequent complication. It may be difficult to differentiate an obstruction from ileus which is part of a generalized peritonitis, the treatment, however, is the same. On the other hand, intestinal obstruction may occur many years after pelvic operations. I am told that gynecologic operations are the most frequent source of intra-abdominal adhesions which eventually produce organic obstruction.

Fecal fistulas may be abdominal or vaginal. Abdominal fecal fistulas are seen most often after difficult operations for removal of residues of

a previous pelvic infection complicated by a tubo-ovarian abscess. Most of these fistulas arise from adherent inflamed portions of the sigmoid flexure of the colon. Consequently, I advocate routine drainage for every patient from whom a chronic tubo-ovarian or an ovarian abscess has been removed. Sigmoidal fistulas of this type usually close spontaneously. Vaginal fecal fistulas are usually of sigmoidal or rectal origin, rarely do they originate in the small bowel. Often they are complications of a severe pelvic inflammatory reaction in the operative field. They usually close spontaneously.

Vaginal Bleeding—Vaginal bleeding following gynecologic operations rarely arises in the perineum. Occasionally it may appear from a suture line in the anterior vaginal wall or from the vaginal vault after hysterectomy. Such bleeding as a rule is not alarming. It tends to stop spontaneously. If it is protracted or unduly profuse, ligation of bleeding points and reapproximation of mucosal margins is indicated.

After cauterization of the cervix it is not uncommon to encounter bleeding on the tenth to the fourteenth day. Occasionally this bleeding is free. It results from a slough of tissues, attempts at suturing are not to be considered. One must depend on rest in bed, a high calcium intake and loose packing of the vagina with gauze to control such hemorrhage. After plastic operations on the cervix it is not uncommon to see severe hemorrhage in five to eight days. Sometimes this stops spontaneously, more frequently it requires ligation of bleeding points.

Unusual bleeding from the fundus of the uterus may occur after removal of an ovary that contains a corpus luteum. If it occurs after a hysterotomy or after a defundation operation, I believe that the blood arises from a sloughing suture line in the endometrium.

Parotitis is extremely uncommon in my experience, attention to oral hygiene and maintenance of the fluid balance may be responsible.

Pain in the lower part of the back (backache) occurs too often. It probably results from strain of the back due to faulty position on the operating table. Local heat, salicylates and time usually control this symptom.

Pulmonary complications may be collapse, pneumonia or infarcts. Collapse is an early complication and should be suspected because of respiratory and cardiac embarrassment. The physical findings are characteristic, the roentgenograms give diagnostic evidence. Ventilation with carbon dioxide and oxygen is specific therapy.

Postoperative pneumonia occurring within the first forty-eight hours is almost unknown in my service.

Pulmonary conditions which appear after a week or later are usually infarcts. They sometimes confirm one's suspicion of cryptic pelvic thrombophlebitis.

PREOPERATIVE AND POSTOPERATIVE CARE IN NEUROSURGICAL PROCEDURES

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The central nervous system differs from other portions of the body in a number of anatomicophysiologic factors which give rise to therapeutic (as well as diagnostic) problems encountered in no other field of surgery. For example, the direct influence of the central nervous system on every organ and part of the body may produce indications for therapy in many portions of the body remote from the central nervous system itself. Further, the position of the central nervous system within the rigid skull and vertebral column not only gives rise to special physiologic problems but makes surgical exposure of the brain or spinal cord and subsequent closure of the wound long, arduous and painstaking tasks.

Such factors, among many others, produce special preoperative and postoperative difficulties which are encountered infrequently, if at all, in other surgical fields. The most thorough diagnostic study and the most brilliant operation may be to no avail if there is any lack of constant observation, meticulous bedside care and appropriate therapeutic measures during the postoperative period. It is with these problems that this paper is concerned. However, it is not my purpose to present a detailed consideration of all therapeutic measures employed in various neurosurgical clinics or to discuss the numerous controversial subjects. Rather, the discussion will be confined to a presentation of those procedures and routines which I have found most satisfactory.

PREOPERATIVE TREATMENT

Observation—The physical condition and the symptoms of a patient with a neurosurgical condition can change very rapidly, and careful observation is an essential feature of preoperative as well as postoperative care. Similarly, observation of the exact pattern of a convulsion may determine the localization of the lesion, or knowledge of a sudden alteration of the patient's blood pressure and pulse rate may alter the plan of therapy.

Symptomatic Treatment—The most common symptom requiring relief is headache due to increased intracranial pressure. The pressure may be reduced to some extent by an occasional saline cathartic (e g, saturated solution of magnesium sulfate, 45 cc), or the headache relieved

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by acetylsalicylic acid or small doses of codeine. Morphine is to be avoided, for it masks symptoms and depresses respiratory function, which is often already impaired by medullary compression. Intravenous injection of 50 per cent sucrose (which is much more satisfactory than dextrose) is sometimes of value in tiding a patient over an acute increase in pressure but is not often indicated in routine preoperative care. Extensive use of hypertonic solutions can be dangerous and is to be avoided.

For the pain of trigeminal neuralgia, codeine or morphine may be given, but these drugs frequently fail to give relief. Trichloroethylene taken by inhalation relieves many patients temporarily. Morphine may be given freely for "spinal nerve root pain."

Many patients are irrational or delirious and require restraint and sedation. If the delirium is mild, phenobarbital or a related barbiturate will be adequate. More severe delirium requires paraldehyde (15 to 30 cc) or chloral hydrate (1 to 2 Gm), administered by rectum. Restraints should be so arranged that the patient's position can be changed easily and at frequent intervals.

If convulsions occur frequently, phenobarbital or dilantin sodium (sodium diphenyl hydantoinate) will usually afford adequate control, but occasionally a status epilepticus requires more heroic measures. Morphine (if the intracranial pressure is not elevated), 1 cc of ether given intramuscularly, tribromethanol in amylene hydrate (avertin with amylene hydrate) given by rectum, or even ether anesthesia may be necessary. A very satisfactory method is administration of a few whiffs of chloroform on a piece of gauze at the first sign of each approaching seizure.

Needless to say, infections of the respiratory tract and other complications elsewhere must be eliminated as completely as possible before operation is undertaken.

Foods and Fluids—As for other types of operation, the patient's state of nutrition should receive careful consideration. Frequent vomiting, paralysis of the muscles of deglutition or the excruciating pain of trigeminal neuralgia may have reduced the patient to virtual starvation. Persistent, frequent small feedings of the patient who vomits frequently and the use of a gastric catheter passed through the nose, left in position and employed for administration of a well balanced high caloric liquid diet are sometimes life-saving measures. Administration of concentrated vitamins is sometimes indicated.

Excessive dehydration is to be avoided, and no effort is made in most of my cases to restrict the fluid intake. For stuporous, comatose or irrational patients an adequate fluid balance should be maintained by gastric tube, by rectum or parenterally.

Bladder and Bowel—The function of the bladder and kidneys may be rapidly damaged by retention of urine. In cases of such damage and in cases of incontinence, an indwelling catheter should be employed, if only for a few preoperative days.

It is important that patients with intracranial hypertension avoid straining at stool because of the resulting rise of venous and intracranial pressure. Constipation should be treated by catharsis and enemas, and the patient should be warned to avoid straining.

Direct Reduction of Intracranial Pressure—In the case of a patient with advanced hydrocephalus and very high pressure due to obstruction by cerebellar tumors, sudden decompression by ventricular puncture followed immediately by removal of the tumor may result in disastrous consequences. Of great value in many such cases is continuous drainage of the ventricles through a metal T cannula with a flat cross bar which prevents its slipping too far into the cranial cavity (Fincher¹). This procedure prevents rapid refilling of the ventricle and enables the brain to become accustomed, so to speak, to a low intracranial tension. It should be employed for four to ten days before the major operation is attempted. The most meticulous care and frequent changes of the quickly saturated dressings are necessary to avoid infection of the ventricle.

Precanesthetic Medication—Most intracranial operations are performed with either local or ether anesthesia. The local anesthesia in many cases is preceded and supplemented by "basal anesthesia," or narcosis induced by either sodium amytal given hypodermically or tribromethanol in amylene hydrate (avertin with amylene hydrate) given by rectum. The latter is to be preferred. It should be preceded by a cleansing enema given at least eight hours beforehand, in order that the bowel may be empty and quiescent when the drug is given. It is given in a single dose of from 85 to 95 mg. per kilogram of body weight thirty to forty-five minutes before the time of operation. If the patient is frightened or irrational, it is well to induce the basal narcosis before he leaves his room or ward and before the head is shaved.

If no preliminary narcosis is to supplement local anesthesia, codeine sulfate (0.065 Gm.) and sodium phenobarbital (0.1 Gm.) may be given hypodermically thirty minutes before operation. If ether is to be used, a preliminary injection of atropine sulfate (0.004 Gm.) should be given.

If the operation is to be a laminectomy, the usual general surgical routine may be followed. Preliminary administration of morphine and atropine is probably the most satisfactory procedure.

¹ Fincher, E. F., Jr. Ventriculography Via Anterior Horns, South M. J. 28: 1082, 1935.

Preparation of the Operative Field—For operations on the spinal cord or on the peripheral nerves, the usual careful shaving and cleansing of the skin and the final application of the surgeon's preferred antiseptic solution are satisfactory. For cranial operations, however, a special routine is advisable. It is wise to clip the hair the day before operation and carefully inspect the scalp for evidence of local infection. The head should never be shaved until immediately before operation, for the many tiny abrasions that occur may serve as fields for the rapid proliferation of pathogenic organisms. Thorough preliminary softening of the hair with surgical soap and warm water is essential. The scalp should be shaved "against the grain" (i. e., the razor strokes should be opposite to the direction of growth of the hair) with a freshly sharpened straight-edged hollow-ground razor.

POSTOPERATIVE TREATMENT²

Shock—At the termination of any serious neurosurgical procedure, the patient's condition must be carefully appraised. The treatment of shock takes precedence over any of the therapeutic considerations to be mentioned. It must be remembered that two factors enter into the picture—hemorrhage and trauma to nerve tissue (Blalock³). If hemorrhage has not been excessive and the systolic blood pressure is between 70 and 90 mm. of mercury, it is safe to wait a short time for spontaneous recovery. If there has been profuse hemorrhage or if the systolic blood pressure is below 70 mm. of mercury, there is only one treatment—immediate blood transfusion. A compatible donor should always be available. Either the direct or the indirect method of transfusion may be used, but it is essential that the blood be given slowly, for a rapid rise in blood pressure may precipitate renewed bleeding in the operative field. The blood pressure should be frequently determined during the transfusion and the injection discontinued when the systolic pressure reaches 110 mm. of mercury.⁴

² It may be well to point out that most of the therapeutic considerations discussed under "Postoperative Treatment" are equally applicable to the care of patients with acute craniocerebral injuries. Such factors as cerebral injury, potential hemorrhage or infection, increased intracranial tension and complications elsewhere in the body are common to both types of case.

³ Blalock, A. Acute Circulatory Failure as Exemplified by Shock and Hemorrhage, Surg., Gynec. & Obst. 58 551, 1934. Blalock, A., and Bradburn, H. B. Trauma to Central Nervous System. Its Effects on Cardiac Output and Blood Pressure, an Experimental Study, Arch Surg. 19 725 (Oct.) 1929.

⁴ The values for blood pressure given here apply to adult patients with preoperative normal blood pressure. Allowance must be made, of course, for preexisting hypertension, the normal low pressure of small children or other deviation from normal adult values. In doubtful cases a marked diminution in pulse pressure may be a valuable indication of the existence of shock.

A patient in shock is usually soaked with cold perspiration. A dry, warm gown and warm blankets should be put on at once. Hot water bottles, if used at all, should be warm, not hot, for the unconscious or anesthetic patient may be burned. Lowering of the head is rarely indicated, because the increased venous pressure within the head may set up fresh bleeding.

Care of the Wound—In dressing the wounds after major cerebral operations, the Cushing ritual of silver foil, gauze and crinoline still proves eminently satisfactory. Thin sheets of silver foil serve as a seal and presumably exert some bactericidal influence. A heavy gauze dressing is then applied, followed by a moist crinoline bandage. The latter is immediately dried by a warm air blower which causes the dressing to shrink and form a snugly fitting cap.

If the operation has been a cerebellar craniotomy, it is essential that no tension be exerted on the muscle suture lines. The head must therefore be fixed in a position of moderate retraction. Heavy body and head casts of crinoline were formerly employed, but it has been found quite satisfactory to use a simple figure-of-eight dressing about the head and neck and to effect retraction of the head with wide bands of adhesive tape extending from the forehead to the lumbar region. Nurses must be cautioned not to twist the neck in turning the patient.

If the operation has been a dorsal or lumbar laminectomy and if any possibility of urinary or fecal incontinence exists, the dressing should be protected from contamination by a sheet of oiled silk or cellophane which is sealed on all sides by collodion or adhesive tape.

If the wound has been drained, if the scar will be visible below the hair line or if there is any fear of infection (as in cases of compound fracture), the dressing should be changed on the first postoperative day. The drain and the skin sutures should be removed and a similar dressing reapplied. Most cerebellar and laminectomy wounds need not be dressed until the fifth day. Healing usually occurs rapidly, and by the sixth or seventh day in most cases dressings can be discarded. The unsightly shaven head may be concealed by a snug cap.

In some craniotomy wounds there will accumulate beneath the edges of the scalp a certain amount of bloody fluid, which is sterile. Wound healing will be promoted by aspiration of the fluid or by insertion of the flat end of a probe and expression of the fluid. The wound should not be opened further, nor should a drain be inserted.

Observation of the Patient—Hemorrhage and Edema. In no field of surgery is postoperative observation more important than in surgical treatment of the brain. This function devolves largely on the nursing service, and intelligent and experienced nursing is essential to successful neurosurgical procedures.

Preferably, the patient on whom craniotomy has been performed should not be left alone for at least twenty-four hours after operation. The blood pressure, the pulse and respiratory rates, the temperature, the state of consciousness and the movements of the extremities should be frequently observed and recorded. Seemingly minor changes should be reported to the surgeon or his assistants without delay, for they may indicate to the experienced observer the development of postoperative hemorrhage or other complications. Restlessness and convulsive movements are signs of cerebral irritation and should never be overlooked.

Observation may be of little value unless it is accurately recorded. Both because of the individual patient's welfare and because of the value of subsequent case studies, it is essential that accurate and detailed records be made of the most minute changes in the patient's condition at the time that they occur.

Careful and experienced judgment is often required to distinguish between the increased intracranial pressure due to postoperative hemorrhage and that due to the swelling that inevitably follows an extensive cerebral operation. Rapid development of coma in a patient previously awake, rapid rise in blood pressure and fall in pulse rate and rapid development of hemiplegia in extremities previously not paralyzed—these signs usually mean hemorrhage. But the "borderline case," with slower and less marked changes, is difficult to evaluate. When grave doubt exists, it is wise to reopen a corner of the wound rather than to risk a fatal termination through failure to evacuate a hematoma. Fortunately, experience renders one's judgment more and more accurate, and technical improvements make postoperative hemorrhage more and more rare.

If hematoma is not present, the intracranial pressure may still become elevated, but the signs will be less marked and less rapid in development. Drowsiness, a gradual elevation in blood pressure and some slowing of the pulse rate usually occur but are not invariable and are not always danger signs (Browder and Meyers⁵). The increased pressure occurring in such cases is usually attributed to "cerebral edema," but actually its true mechanism is unknown (Pilcher⁶). Frequently no specific treatment is necessary, but in cases of severe involvement several measures are useful. The occasional use of hypertonic solutions (50 per cent sucrose given intravenously or 50 per cent magnesium sulfate given by rectum) may be of value. If the ventricles

5 Browder, J, and Meyers, R. Observations on Behavior of the Systemic Blood Pressure, Pulse and Spinal Fluid Pressure Following Cranio-Cerebral Injuries, *Am J Surg* **31** 403, 1936

6 Pilcher, C. Experimental Cerebral Trauma, *Arch Surg* **35** 512 (Sept) 1937

are dilated and a suitable opening in the skull is already present, ventricular puncture will reduce the pressure. After the removal of cerebellar tumors, spinal puncture is both efficacious and safe, for the posterior wall of the foramen magnum and usually the arch of the atlas have been removed, and hence the danger of herniation of the brain stem cannot exist.

Drugs—For reasons already stated, morphine may be dangerous and should rarely, if ever, be employed. Patients have surprisingly little pain after craniotomy, and this is usually easily controlled by small doses of codeine given hypodermically. It is well to avoid oral medication during the first twenty-four to thirty-six hours, since undesirable vomiting may be induced.

Stronger medication should not be employed until the patient has been seen by the physician, for undue restlessness may be a danger sign. Phenobarbital or, rarely, paraldehyde or chloral hydrate given rectally may be necessary to subdue a delirious patient.

To patients who have previously had convulsions it is wise to give small doses of phenobarbital twice a day for several weeks or even months, for the already hypersensitive cortex may be further irritated by the trauma of operation, the subsequent healing process and the contracture of the cerebral scar.

Of course, morphine or other analgesic drugs may be safely given to patients after operations on the spinal cord.

Fluids and Food—A fluid reserve depleted by profuse sweating, loss of blood and abstinence during a prolonged operative procedure should be early restored. In my own cases, 2,000 cc (for adults) of physiologic solution of sodium chloride is given immediately by hypodermoclysis. Oral administration of fluids may be begun as soon as the patient's state of consciousness or postanesthetic nausea permits. Soft or even solid food can often be taken, and, if so, should be given, within eighteen or twenty-four hours of the operation. Irrational or comatose patients should have feedings begun by gastric tube within twenty-four to forty-eight hours.

Many neurosurgical patients must be coaxed to eat, often they must be fed, and again painstaking nursing care is essential. The patient's dietary preferences and dislikes must be indulged. There are no dietary taboos, nor should fluids be restricted below an average level in most cases.

Care of the Bladder—The bladder presents a serious postoperative problem in many of the neurosurgeon's cases, particularly after operations on the spinal cord. Several types of disturbance of the bladder may occur.

Simple incontinence in irrational patients merely requires frequent changing of bed linen and is usually a temporary complication. If

involuntary urination is frequent an accompanying retention of urine will usually be found. Immediate postoperative catheterization (with or without incontinence) must be watched to insure that it is satisfactorily managed by a few catheterizations at intervals of four to twelve hours. It should be mentioned that a frequently overlooked cause of sudden elevation of the bladder is a frequently overlooked cause of sudden elevation of the bladder which may mistakenly be thought to be due to an increase in the volume of urine.

If retention is expected to persist for more than a few days an indwelling catheter should be inserted and connected with a 'tidal drainage' apparatus of Munro.⁷ This prevents infection of the bladder and provides automatic irrigation.

If retention will probably be permanent (as in the case of lesions of the cord) an automatic, or "cord" bladder, should be permitted to develop, which has a permanent residual urine capacity which "overflows" at intervals, when a certain level has been reached.

Suprapubic cystostomy should be performed when permanent incontinence with dribbling or a large amount of residual urine is present or when infection of the bladder fails to respond adequately to treatment.

All catheterizations should be performed with the most meticulous aseptic technic, for renal infection is a frequent terminal event in such cases. Frequent cultures of the urine and determinations of renal function are necessary.

Care of the Bowel—Constipation is highly undesirable in neurosurgical conditions. Enemas should be used freely after the first postoperative day, and mild cathartics, such as aromatic cascara or magnesium citrate, may be employed on the third day and thereafter in most cases. Fecal impactions are frequently encountered, especially in cases of disease of the cord, and an unsuccessful enema should call for immediate rectal examination. Regular administration of liquid petrolatum is helpful in reestablishing normal action of the bowel.

Care of the Skin—In no field of medicine is good nursing more important than in the care of the skin of a paralyzed and anesthetic patient who may be both incontinent and comatose and is often emaciated. His position should be changed not less often than every hour, the skin over every bony prominence should be frequently but gently massaged with some bland lubricant (such as zinc oxide or boric acid ointment) or simple petroleum jelly) and subsequently powdered. Pressure on the skin should be prevented as far as possible with a rubber ring under the sacrum or hip, gauze "doughnuts" under the

⁷ Munro, D. Tidal Drainage of the Urinary Bladder, New England J. Med. 212: 229, 1935.

ankles, heels and lower part of the knee and a pillow between the knees. Bedlinen must be kept dry. Hot water bottles should never be used in the presence of anesthesia. "Air mattresses," which may be inflated to any desired degree of firmness, are of great value in difficult cases.

Even with the best care, decubitus ulcers sometimes develop. These should be dressed with the greatest care, sloughing tissue debrided and the edges of the skin protected with zinc oxide paste or a similar ointment.

Other Problems—Many other postoperative problems arise, only a few of which can be mentioned briefly here.

If the cornea is anesthetic (and particularly if an accompanying peripheral paralysis of the facial nerve prevents closure of the eye), the eye must be kept closed with a firm cotton pad, with a collodion seal of the eyelashes to the cheek or, if necessary, with actual suture of the eyelids.

Postoperative pulmonary complications occur infrequently in neurosurgical diseases but should be guarded against by suction of mucous accumulations from the pharynx and frequent changes in the patient's position. The lips and tongue of an unconscious patient should be lubricated with liquid petrolatum.

Spastic extremities are saved from contracture by appropriate application of heat, massage, passive motion and similar physical therapeutic measures. The patient should be got out of bed and encouraged to move about as soon as the wound and his general condition permit.

Reeducation of mind, of speech or of muscles is sometimes necessary. Of great importance are encouragement and reassurance of the patient, whose dangerous and harrowing experience may have reduced him to a state of pitiable fright or somber depression. Long-suffering patience and tolerance are often necessary in both physician and nurse, but it should never be forgotten that the patient's aberrations, carelessness, language or actions may be of organic neurologic origin and completely beyond his control.

PREOPERATIVE AND POSTOPERATIVE TREATMENT IN UROLOGY

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The aim of preparation of patients for operation is restoration as near to the integral state as possible, and this consists in correction of physiologic and chemical abnormalities and in increasing reserve capacities. Thanks to the many experimentalists who have provided theory basal to the clinical management of the sick person, modern treatment rests largely on a logical basis, and empiric practices each year become fewer. It is axiomatic that greater certainty and predictability, and hence efficiency, attend management based on the correction of pathologic mechanisms, with irrational and intuitive method eliminated as far as possible. A second desideratum is simplification of therapy, since it is obvious that more abracadabra accompanies unduly complex procedures. The following methods of treatment, then, are intended to be as simple as the correction of chemical aberrations due to disease will permit. It is hoped that no impression of finality will be derived from the apparently categoric way in which these methods are described.

SPECIAL PROBLEMS IN UROLOGY

There are three factors which make the treatment of urologic patients a special problem, otherwise, the preparation does not differ from that of other types of surgical patients. The special features of urologic surgery are these. The kidney, which is so often disturbed in disease of the urinary tract, is the chief organ of the body for elimination of nonprotein nitrogenous metabolic products, of nonvolatile electrolytes and of water, so that interference with renal function leads to retention of these substances and at times of pressor substances. Second, absorption of bacteria from the urinary tract, with septicemia and the accompanying chill and other manifestations of infection, is frequent, metastasis of infection, however, is rare, and the common invading organisms, *Escherichia coli* and closely related bacteria, are of low pathogenicity to man. Third, the majority of the patients is at a senile age, so that the management of aged men comprises a large part of the practice,

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recalling James Hilton's description of Mr Chips "Nothing really wrong with him—only anno domini, but that's the most fatal complaint of all, in the end"

Drugs—As is consistent with the ideas outlined in the first paragraph, reasonably efficient management of patients can be carried out with use of only a few drugs. These are the alkaloids, morphine, atropine, digitalis and quinidine, the barbiturates, a few simple chemicals, such as sodium chloride, sodium bicarbonate (50 per cent), Ringer's solution, lactate buffers and 5 per cent dextrose, for intravenous use, chemotherapeutic agents, sulfanilamide and, in cases of pneumonia, sulfa-pyridine, posterior pituitary, transfusion of blood, and for irrigation with antiseptics, sodium chloride (0.9 per cent) and boric acid. Considering the use of local antiseptics for purposes of irrigation, the classic paper of Fleming¹ is referred to, the differential between bacterial injury and tissue damage is often so small that strong antiseptics frequently cause more harm than good. Since preservation of correct osmotic relation is the constant activity and necessity of the cell, the use of any irrigating fluid must be considered from the standpoint of tonicity, and use of an isotonic fluid must be stressed. It should be pointed out that the rather widespread use of such drugs as methylthionine chloride U. S. P. (methylene blue), sandalwood oil, hexamethylenetetramine (methenamine [urotropin]) and the majority of the so-called urinary antiseptics is not supported by available evidence as to their efficiency.

Renal Insufficiency—It has repeatedly been demonstrated that the most satisfactory results of treatment of uremia are observed in patients with obstruction of the urinary tract. The implication is clear to provide free drainage by the use of the catheter in these cases. In cases of obstruction of the lower part of the urinary tract two devices for drainage are available, the urethral catheter and suprapubic cystostomy. The use of each is accompanied by a foreign body purulent reaction and infection, a difference exists in that the urethra is in close proximity to large vascular sinuses in the corpora cavernosa, through which infection of the blood stream occasionally results. Drainage with a urethral catheter (no. 18F) is usually highly satisfactory, but when signs of intolerance, such as fever, occur suprapubic cystostomy should be resorted to. This operation, done through a high incision only large enough to give good exposure of the bladder, can be carried out with nearly negligible mortality rate. It has been a question whether all of the urine can be safely evacuated from the chronically overdistended bladder at one time or whether slow decompression should be employed. The argument has

¹ Fleming, A. Action of Chemical and Physiological Antiseptics in Septic Wounds, *Brit J Surg* 7:99, 1919.

recently been discussed critically by Creevy,² who has stated the opinion that sudden emptying is not dangerous. We agree with this opinion.

In cases of anuria, unless it is certain that nephritis uncomplicated by obstruction is the cause, ureteral catheterization should be resorted to. It need not be emphasized that intravenous urographic procedures in uremic patients are strongly contraindicated because of the disturbed osmotic relations in the blood serum caused by introduction of the contrast medium. The work of Helmholtz and Bollman³ on the deleterious effect of hypertonic solutions of sugar on the kidney may be recalled in this regard. Intravenous pyelographic procedures similarly have caused a complete excretory shutdown in patients with renal damage.

It has been repeatedly observed in clinical patients with chronic renal insufficiency, as well as in experimental animals (especially certain fishes) that retention of nonprotein nitrogenous bodies is not incompatible with good health. Uremia in the clinic must be considered essentially in terms of acidosis and dehydration, and simple chemical methods are available for assay of these conditions, namely, determinations of the p_H , of the carbon dioxide content or capacity and of the amount of water present in the plasma.

Acidosis—Lowering of the p_H in cases of uremia occurs for at least two reasons: first, because in the uremic patient the food intake approaches the starvation level, depleting the glycogen supplies and thus, through interference with fat metabolism, leading to an accumulation of acid products, and second, because of the reduced elimination of fixed acid radicals, notably phosphates and sulfates, which are set free from organic breakdown in metabolism without corresponding base coverage. While the kidney is not damaged by a lowering of the p_H as it is in the presence of a corresponding alkalosis, the general status of the body urgently demands correction of the acidosis. It should be pointed out that both carbon dioxide content or capacity and p_H values are necessary to indicate the acid-base status of the patient; it is obvious that a reduction in carbon dioxide content occurs both in acidosis and in the respiratory type of alkalosis associated with hyperpnea (e.g., hyperventilation from a pneumonic process) and that determination of the hydrogen ion concentration, for which simple methods are available, is necessary to point out the direction of the carbon dioxide shift.

There are several ways in which acidosis may be corrected, the most important being the establishment of free drainage. Chemical aids include parenteral administration of sodium chloride (0.9 per cent or of

² Creevy, C. D. Is Sudden Emptying of the Chronically Distended Bladder Dangerous? *J. Urol.* **39** 403, 1938.

³ Helmholtz, H. F., and Bollman, J. L. Diuretic Action of Sucrose and Other Solutions, *Proc. Staff Meet., Mayo Clin.* **14** 567, 1939.

sodium bicarbonate (say 300 to 500 cc of 5 per cent sodium bicarbonate) or of solutions⁴ like the Haitmann-Ringer buffer⁵ (500 cc) It is inadvisable to give large amounts of the latter two substances unless further determinations of the p_H and the carbon dioxide content are made The mode of action of isotonic sodium chloride, which is neutral in reaction in relieving acidosis, is of interest and is explainable by the Hamburger chloride shift phenomenon Owing to the impermeability of the erythrocytes to sodium ion, chloride migrates into the red cell, where it is buffered by the hemoglobinate present, leaving the excess sodium to combine with carbonate to increase the bicarbonate of the plasma Dramatic improvement is seen frequently following the correction of acidosis which, to repeat, must be controlled by frequent assays of the blood

Fluid Balance—In addition to the advantages of isotonic sodium chloride solutions for the correction of acidosis fluid balance is of importance because of the beneficent effect of diuresis in ridding the body of catabolites and for purposes of internal irrigation of the subrenal portion of the urinary tract

The important studies of Collier and Maddock⁶ on the quantity and type of fluid needed have been of clinical value Briefly, these workers found that insensible loss of fluid in the adult patient amounts to 1,000 to 2,500 cc daily, the difference being related to fever This amount needs to be replaced, together with enough fluid to eliminate an estimated 35 Gm of catabolites excreted in the urine, the output of which they estimated as about 1,500 cc, together with an amount equivalent to compensate for unusual losses as in vomitus or the stool For most patients an intake of 3 to 4 liters of fluid daily will be found adequate, but in states of dehydration this amount should be exceeded A second point of importance emphasized by Collier and Maddock is the undesirability of giving excesses of sodium chloride in parenteral fluids, which may induce retention of water as a result of excess accumulation of salt, correction of this situation may be brought about by substituting isotonic dextrose (5 per cent) in distilled water if water cannot be taken by mouth

4 Hartmann, A F, and Elman, R The Effects of Loss of Gastric and Pancreatic Secretions and the Methods for Restoration of Normal Conditions in the Body, *J Exper Med* **50** 387, 1929

5 The composition of this fluid in millimols per liter of water is sodium chloride, 95, potassium chloride, 5, calcium chloride, 2.5, and sodium lactate, 25

6 Collier, F A, and Maddock, W G A Study of Dehydration in Humans, *Ann Surg* **102** 947, 1935 Collier, F A, Dick, V S, and Maddock, W G Maintenance of Normal Water Exchange with Intravenous Fluids, *J A M A* **107** 1522 (Nov 7) 1936 Maddock, W G Fundamentals in Water Balance, *J Urol* **39** 444, 1938

Excess hydration can be detected in clinical patients by examination of hypostatic regions, such as the sacrum and extremities for pitting edema, by the presence of edema of the lungs and by determination of the amount of water in the plasma. Plasma water is maintained at a rather constant level, and changes reflect dehydration and hyperhydration of the patient, as has been found by Eichelberger in studies on the dog with uremia from hydronephrosis.

Infection—We have been impressed favorably by only two methods of aid to the patient in overcoming infection of the urinary tract, namely free drainage of a locus of infection and chemotherapy with sulfanilamide. No other therapeutic agents have been of unequivocal clinical benefit. The use of ketogenic agents and of mandelic acid as urinary antiseptics is regarded as drastic because of the accompanying acidosis. It has been found by many observers that sulfanilamide will not disinfect the urinary tract in the presence of calculi.

Gastrointestinal Ileus—One of the most troublesome complications in urologic surgical procedures is paralytic distention of the bowel. This condition is seen after every operation on the kidney, is distinctly less common after suprapubic operations on the bladder and prostate and is uncommon after transurethral resection of the prostate. This constant complication of renal operations, occurring independently of the type of anesthetic agent used and when the peritoneal cavity is not opened, seems to be caused by reflex action.

Acute dilatation of the stomach with massive retention of liquids is regarded as of great risk to the patient because of the danger of aspirating vomitus, which is an important cause of death by drowning or of pulmonary infection. The incidence is perhaps greatest in patients after spinal anesthesia who drink large quantities of fluids. The most satisfactory treatment is introduction of a stomach tube immediately the first suspicion of the condition has been aroused, followed by aspiration with the Wangenstein⁸ type of gastric suction.

Apparently adynamic intestinal ileus rarely is of great clinical significance, as a rule it merely produces abdominal pain and discomfort. We have found the following methods to overcome paralytic intestinal distention more effective than others. When gas is present during the first day following operation, application of heat to the abdomen and insertion of a catheter in the rectum, after the first postoperative day, injections of solution of posterior pituitary of twice U. S. P. strength

7 Eichelberger, L. Experimental Hydronephrosis in Dogs. *J. Urol.* **46** 366, 1938.

8 Wangenstein, O. H. Early Diagnosis of Acute Intestinal Obstruction with Comments on Pathology and Treatment, with Report of Successful Decompression of Three Cases of Mechanical Bowel Obstruction by Nasal Catheter Suction Siphonage. *West J. Surg.* **40** 1, 1932.

1 cc subcutaneously, followed in exactly ten minutes by an enema consisting of 30 Gm of magnesium sulfate, 60 cc of glycerin and 90 cc of water, these to be repeated after eight hours when necessary

Transurethral Resection of the Prostate Gland—For this special procedure elaborate preparation is not needed unless the patient is suffering from uremia, dehydration, fever, cardiac disease or some other nonurologic complication. When the bladder apparently has been distended for a long period or when the urine is heavily infected, drainage by indwelling catheter is resorted to for several days. Otherwise no preparation is needed. In this regard it should be recalled that all operations on the prostate gland in cases of benign prostatic hypertrophy are operations of election and never of necessity, prostatic operations, then should never be done on a patient bedridden because of this disease.

Postoperative complications peculiar to resection are retention of urine, bleeding and infection. These complications occasionally develop when a seemingly adequate operation has been done. It has been our policy to leave a catheter indwelling in the urethra for two or three days after resection, depending on the amount of blood in the urine, when the urine is grossly free from blood, the tube is removed. In a considerable number of patients with high grade retention the urinary flow is inadequate or nil after the first resection, a urinary stream of large caliber is of as great importance as the amount of urine retained in deciding whether further resection is indicated. If the flow is not adequate within forty-eight hours resection again is indicated unless the patient is febrile, which indicates drainage by catheter. When there is still significant obstruction two days after removal of the indwelling catheter after the first resection, nothing is to be gained by further delay.

Hemorrhage usually is an unimportant complication of resection. The most important control of hemorrhage is necessary at the time of operation. Secondary hemorrhage is not infrequent, however in the period from the tenth to the twenty-fifth day and in our experience is unimportant except that retention may occur from clotted blood, such episodes have been treated with an indwelling urethral catheter for several days until the bleeding has stopped. Coagulation of the bleeding points with the resectoscope, the use of hydrostatic bags (Foley type) and cystotomy have not been necessary in this clinic.

Infection of the bladder apparently always follows transurethral resection but usually promptly clears up or remains clinically negligible, producing no symptoms, provided resection has been adequate. Chemotherapy with sulfamylamide (0.6 Gm four times daily for five days) is used if there is constitutional reaction to infection and for patients with pyuria, for eight weeks after resection. Aside from a mistaken or incomplete diagnosis, persistent infection has usually been found asso-

ciated with retention of a fragment of tissue, inadequate resection or calculous incrustation of a portion of the prostatic bed.

CONCLUSION

Again it should be stated that these methods of treatment are not in a final, finished form and that there is opportunity for improvement in every branch of surgery. Also we would emphasize that in common with experiences in other branches of surgery postoperative complications can be reduced materially by technical finesse in the conduct of the operation.

PREOPERATIVE AND POSTOPERATIVE CARE IN RECONSTRUCTIVE SURGERY

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Attention to the special details of preoperative and postoperative care may make the difference between success and failure in plastic operations. This requires the cooperation of an enthusiastic and well trained surgical house staff and nursing staff plus a great deal of personal care by the surgeon himself.

PREPARATION

The patient should be examined carefully for possible cutaneous infections, as a small pimple anywhere on the body may be a contraindication to operation.

Routine laboratory work should be done, but if there are multiple admissions close together this may be slackened somewhat. The clotting time and bleeding time should be noted in all cases in which extensive procedures are to be undertaken and especially if there is to be much undermining, as in raising a large flap. Steps should be taken to correct any abnormalities in the clotting time if possible, if not, the operation should be delayed.

Sedation the night before operation is advisable, and the patient may be allowed to sleep as long as he can in the morning before operation. If the usual enema is unnecessary, it may as well be omitted.

Preoperative Fluids and Extra Carbohydrates—These may be given freely if long procedures with general anesthesia are to be carried out. If local anesthesia is to be used, fluids may be allowed up to one or two hours before operation.

Local Preparation—Local preparation is important in respect to saving time in the operating room. Soap and water cleansing of the area plus appropriate shaving is usually enough, but if a skin graft is to be put on the face or neck it may be best not to shave the thigh or abdomen to avoid transferring any undesirable hair-bearing skin.

About the face and scalp it is well to have the hair freshly washed before operation and then to shave only minimum amounts. Eyebrows

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are practically never shaved, as they require a long time for regrowth, and the absence of one gives a very unsightly appearance. Men should be shaved on the morning of operation.

Preoperative Drugs—The choice of drugs is so much a matter of individual preference of the surgeon and often of the patient that no universal routine can be established. Large doses of morphine are not given to any patient, especially to a child who is to have an operation on the mouth or neck and who may have difficulty in breathing.

General conduct in the operating room, especially with the operative region under local anesthesia, can be guided by common sense and caution. Conversation and all noises may as well be at a minimum. A modulated voice. The patient should not be used for a table or rested on by the operator or assistants.

Antiseptics—It is desirable that the patient come to the operating room as generally clean as possible. As has been noted, the scalp should be freshly cleaned, men should be shaved, and then soap and water cleansing may be all that is required. As a time-saving expedient and perhaps for some sense of security, a mild local antiseptic may be used, and 1 to 3 per cent iodine usually suffices, although many of the proprietary solutions seem to give adequate protection in the hands of other operators.

Local Anesthetics—The kind of anesthetic used is a matter of the surgeon's choice, but a few rules are important. Epinephrine hydrochloride is used in sufficient amounts to hold the anesthetic but is kept to a minimum in raising flaps—in fact, most large flaps are raised with the patient under general anesthesia. Extreme caution should be used in injecting the solutions, and there should always be an accurate understanding between the nurse and the operator about the percentage of anesthetic and the amount of epinephrine hydrochloride being used. It is best to rely on the patient's word about the success of the anesthetic, as on this may depend the success of the operation.

POSTOPERATIVE CARE

Postoperative care may be said to begin with the operation. Gentleness in handling of tissue cannot be too often stressed, and wounds firmly closed, with no dead spaces and with a minimum of surface scratches, heal best and make the postoperative care easier for all concerned.

Dressings—In plastic operations, dressings are frequently as important as any operative step, and therefore sufficient time should be taken to get them exactly right. Pressure dressings over grafts flaps and most wounds are necessary and are actually more comfortable than

loose dressings that might slip. All blood is cleaned away, fine mesh grease gauze is smoothed carefully over the wound, and a medium of pressure is applied and fixed with the final bandage and adhesive tape. This medium of pressure may be soft, "wool-form" sterile marine sponges or soft cotton mechanic's waste (figs 1 and 2). Other materials have been used successfully but the final bandaging really produces the pressure and should be meticulously done. It has been possible to

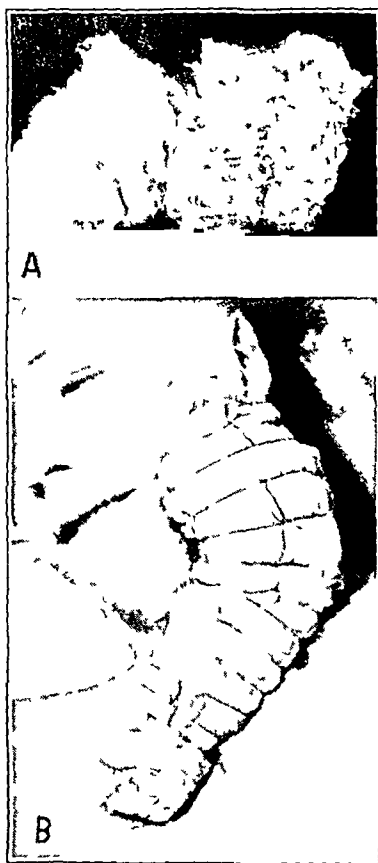


Fig 1—*A*, two kinds of soft cotton mechanic's waste used as a medium of pressure in surgical dressings. *B*, use of coarse waste to hold a graft on the neck; sutures from the edges are tied over the surface after one gauze sponge has been used to cover the waste.

do a complete replacement of the axillary skin in an area of over 100 square inches (645 sq cm), to allow the first dressing to remain in place eight days and to have only one other while the patient was in the hospital (fig 3).

Pressure on Surgical Wounds—The value of pressure has been recognized for a very long time, there being several references to it in



Fig 2—4, B and C, application of a waste dressing over a split graft. D, E and F, dressing of the donor site of a split graft. The deep green culture left in place twelve days. G and H, final fixation of the waste with sutures and of the joint with plaster of paris.

the hieroglyphics translated in "The Edwin Smith Surgical Papyrus"¹ regarding treatment of wounds of the nose and ear

Immediately after operation, if there is any doubt about the patient's condition, some responsible person, the surgeon or the anesthetist, should remain close by until the patient can safely be turned over to the nurse. Blocked airways and continued hemorrhage may occur after operations about the mouth, and the patient is turned on his abdomen or side so that the fluids can run out, preventing choking. Mouth gags and towel forceps for pulling out the tongue should be on hand in all



Fig 3—Simple fixation of a large axillary graft with a pressure dressing reenforced with a simple bed pad as shown folded under the left arm. This usually suffices and eliminates the necessity of a heavy plaster of paris fixative device

questionable instances, but a short McGill tube inserted through the nose and over the tongue block and held just above the glottis will usually suffice if its position can be maintained

Postoperative Sedatives—Sedation is important, but usually not until the patient has completely reacted. Sedatives are not given for

¹ Breasted, J. H. The Edwin Smith Surgical Papyrus. Published in Facsimile and Hieroglyphic Transliteration with Translation and Commentary in Two Volumes, Chicago, University of Chicago Press, 1930

tight bandages or for pain in the eye which is under a dressing, but the cause of discomfort is searched for and relieved

Water—Water may be given early by mouth and vomiting permitted if it does not interfere with dressings or wounds. Many times it may be found that ten to twelve hours after operation fluids have been withheld by a nurse cognizant mainly of abdominal surgical routine.

Diet—The diet may be increased rapidly except, of course, when contraindicated by procedures about the mouth.

Liquid Diet—A liquid diet is often necessary and may be given by mouth or through a feeding tube. The daily ration is about 2,500 calories for adults, and it has been noted that there is apt to be too much carbohydrate in the diet. The diet outlined here has been used successfully for several years and gives a fairly good balance.

Protein	75 Gm	300 calories
Fat	160 Gm	900 calories
Carbohydrate	350 Gm	1 400 calories
		<hr/> 2 600 calories

	Ounces	Cc	Protein Gm	Fat Gm	Carbohydrate Gm	Calories
Six eggs	6	180	36	30		450
Cream (20 per cent)	8	240	8	45	5	450
Milk	24	720	24	24	45	450
Tomatoes (strained, canned)	6	180	3		6	36
Dextrose, Karo, dextrin or lactose	10	300			300	1 200
Salt	1 teaspoon					
	<hr/> 54	<hr/> 1 620	<hr/> 71	<hr/> 102	<hr/> 362	<hr/> 2 646

This may be given as a mixture to simplify the procedure and be sure the patients get their full ration, but whenever possible the ingredients should be used as a daily ration, with individual dishes nicely prepared and as appetizing as possible. Many attractive dishes can be prepared, and flavors, chocolate, fruit juices, ice cream, etc. can be added as desired. Dr. Ellsworth Smith has reported the use of this ration for 1 patient steadily for over two years.

At least two oranges or lemons as sweetened fruit juice should be given between feedings each day, and the patient may have all the water, coffee, tea, fruit juice, ice cream or other special food that is permitted.

If a fuller protein ration is desirable, lean scraped beef or fresh beef juice may be added.

If there is too much volume to get down in twenty-four hours, 6 ounces of Dryco may be substituted for the 24 ounces (720 cc) of milk. For further reduction, the vegetable juice or the beef juice may be temporarily omitted.

Hygiene of the Mouth and Nose and Prevention and Treatment of Parotitis—Cleaning the teeth with a soapy dentifrice and simple mouth washes or one-half strength hydrogen peroxide is encouraged. Infants' mouths may be difficult to clean but should be carefully swabbed when necessary.

The prevention of sordes will do most to prevent parotitis. When parotitis does occur, frequent stimulation with candy or lemon juice each half hour, chewing gum and occasionally the use of pilocarpine hydrochloride, $\frac{1}{20}$ grain (3 mg) every four hours, is recommended for adults. External heat and roentgen treatment may be used early, and probing the duct once a day may help a good deal. This type of parotitis rarely needs the external drainage advocated by others.

The nasal airway should be kept open with simple cleansing and medication if necessary.

CLEFT LIP ROUTINE

The cleft lip may be corrected (over the open alveolar cleft if present), even in the first twenty-four hours of life. During the period of jaundice, when the clotting time may be prolonged, and if there is much loss of weight operation is delayed. It is quite certain that operation just after birth is more difficult than at several weeks or months of age, and therefore one who does the operation infrequently may expect better results from waiting until the child has gained a little size.

As for all patients with disease requiring operation thorough physical examinations are necessary. Cutaneous infections and infections of the respiratory tract, as well as prolonged clotting or bleeding times, are contraindications for operation. Feeding should be allowed to within four to six hours and water to within two hours of operation.

It is possible to induce basal anesthesia with some barbiturate or with avertin with amylene hydrate and to do the entire operation with this and procaine hydrochloride. The patient, however, is so apt to wriggle around on the operating table that some ether may be necessary.

Postoperative Care—After operation the baby is put in the care of a special nurse and is kept in the operating room until awake from the anesthetic and until it is certain that the airway is open, that bleeding has ceased and that shock is not present. Tap water is given by rectum and, if necessary, saline solution is injected under the skin. Five per cent dextrose water is brought to the operating room and given in small amounts as soon as the child can swallow. This has been found to be an excellent sedative for infants, and several ounces of fluid may be given soon after operation.

The patient is placed on the abdomen to allow blood to run out of the mouth and the continuance of hemorrhage is closely watched for. A stitch which is put through the tongue at the start of the operation,

is left in and gives a good way of maintaining control of the tongue and therefore the airway while the patient is waking. For infants and children this stitch is left in throughout the first night.

When fully awake and in satisfactory condition the patient is returned to the ward. Airways must be kept open and possible hemorrhage must still be watched for. If the nostrils are occluded infants may fail to breathe properly because they simply do not make an effort to hold the lower lip out of the way and this may be guarded against by strapping the lip down with adhesive tape or by putting a small rubber tube in the mouth and fastening it to the cheeks with adhesive tape.

Immediate attention is given the lip. It is kept clean of blood and mucus by gentle wiping with small gauze squares soaked in a solution of equal parts of alcohol and boric acid solution. This is especially important during the first few hours, as the blood serum that oozes out at this time, if allowed to remain will make a very hard crust over the suture line. If crusts do form, they are loosened by wet packs or cold cream and then gently separated from the stitches. If there is superficial cellulitis or infection around the suture line wet packs should be carefully applied. The lip is usually protected from trauma and from muscle pull by a modified Logan clamp held on with adhesive tape. A small, firmly applied dressing of fine mesh grease gauze, a small pad and final fixation with plain or elastic adhesive tape are sometimes substituted for the exposed wound technic.

Feeding is started early and for the first twenty-four to forty-eight hours is done with a sterile syringe with a rubber tip or with a spoon. After this the baby may nurse the breast if there is a question of maintaining lactation. Water by mouth may be given as soon as the child will take it. The utensils should be sterilized to prevent contamination from other patients. (In repair of palates, nipples are withheld for three weeks after operation.)

The patient's hands must at all times be kept away from the mouth. For infants, a special cuff of wooden tongue depressors sewed into cloth is tied around the arm. For older children (and adults if necessary) padded anterior wooden splints are applied to prevent flexion of the forearm.

The skin sutures are removed in four or five days and the deep sutures in eight to twelve days.

CLEFT PALATE ROUTINE

The preoperative and postoperative care when the palate is being repaired is practically the same as that used for repair of the lip. The operation is done later in life, respiratory infections are more important to guard against and the operation carries some chance of postoperative death, whereas deaths following operations on the lip are practically

nil During bad weather and while infections of the respiratory tract are prevalent it may be best to withhold operation

There should be nothing in the stomach at the time of operation, and therefore if the baby has inadvertently been given milk one or two hours previously operation should be delayed

After operation the patient is allowed to recover in the operating room, and the same routine for administration of fluids and for maintaining the airway is followed as in the operation on the lip except that no airways should be put in the mouth The stitch in the tongue should be used to hold the tongue out constantly if necessary Food and fluid may be given early, but no solid foods should be given for three weeks It is especially important to keep nipples, spoons and fingers out of the mouth Water should be used in an attempt to clean the palate after each feeding Suitable nasal drops may be used several times a day to keep down swelling and to apply some mild antiseptic to the cavity and the upper surface of the palate

The packs in the lateral incisions are removed in twenty-four to forty-eight hours and the sutures in three weeks If the child is intractable, it may be necessary to give an anesthetic for this

Loss of weight may be expected in all instances, because the mouth is so uncomfortable that the patient does not wish to swallow anything This requires persistence in feeding and attention to all details that will hasten healing

Otitis media is a frequent complication in repairs of the lip and of the palate and must be watched for and treated In many instances incipient or actual otitis is found in the preoperative examination, and if it is acute the operation is, of course, delayed Although otitis was fairly frequent in a large series of patients, none of them had severe mastoiditis

Postoperative Elevation of Temperature—This symptom following repair of a cleft palate, when not due to infection of the ear or of the lung is probably due to infection in the nose involving the nasal surface of the palate If this infection continues over several days, there is probability that the suture line will not hold in some area and that an opening will persist in the palate Combating this condition is difficult, but except for gentle cleansing and suction of the discharge and application of mild antiseptics, together with medication to shrink the membranes, little can be done Sulfanilamide of course may be given if it is felt that it will cause no bad effect on the healing of the fine suture line

CARE OF RAW AREAS (BURNS, ULCER OF THE LEG ETC)

General Care—The general care of the patient is of primary importance and includes the exercise of patience and gentleness, interest in the surroundings should be developed, especially when the patient is a child Nutrition must be kept up and transfusions may be required frequently

Local Care—The care of open wounds has for its object the cleaning up of the areas as quickly as possible, so that the lost surface may be restored with skin grafts before damaging contractures have occurred and before debilitation and pain have developed beyond control. Surgical drainage may be accomplished by the use of saline dressings or by the continual saline bath for from one to three hours a day followed by

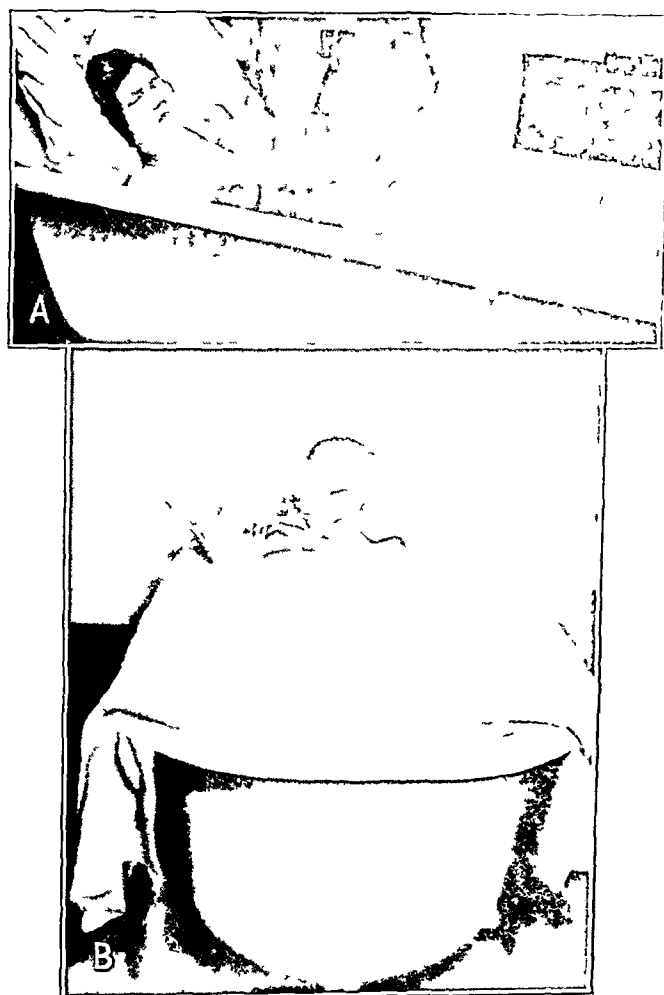


Fig 4—*A*, debridement of the wound with the patient in a saline bath. *B*, patient with a severe burn of the leg who has started occupational therapy for burned contracted fingers even before operation.

application of dry heat or further wet dressings (fig 4). Many antiseptics, common and proprietary, and gentian violet may be used but diluted solution of sodium hypochlorite (Dakin's solution) is usually relied on if anything other than saline solution is thought necessary.

A firm pressure dressing that is kept moist by irrigation and combined with elevation of the part may be of great advantage especially for

lesions of the extremities, marked improvement may be noted within forty-eight hours. It is possible to change edematous, spongy bluish granulations to a good, red firm base by use of pressure so that the granulations do not have to be cut down or burned with silver nitrate.

Pain should be kept down to a minimum when the dressings are removed, and they may be soaked off gradually in a bath. It is important that some protector be used next to the wound to prevent the granulations from growing up through the coarse meshes of the usual surgical gauze. For this, old linen, perforated cellophane-like material or very fine mesh gauze is usually satisfactory, so that dressings can be removed even from children with a minimum of discomfort. (It is felt that the routine use of fine mesh gauze over all open wounds is a very important point in this work.) When cellulitis is controlled, grease dressings (bismuth tribromphenate [xeroform] 4 per cent zinc oxide 5 per cent merthiolate ointment 1:2,000 or scarlet red 5 per cent) on fine gauze or linen may be used, these allow the patient greater freedom, but they are usually not used for several days immediately preceding operation. Plain petrolatum is not used because it is apt to cause maceration. Gentle mechanical cleansing of wounds daily with soap and water is important in keeping crusts and dead tissue cleared away but care should be taken not to disturb epithelization. There are so many ointments in current use for wounds that they all cannot be included here (cod liver oil, paraffin, sulfhydryl-containing compounds, allantoin, mercurials). Application of sulfanilamide or of one of its derivatives directly over the raw areas may be indicated at times.

Surgical drainage and pressure dressings usually produce bright red, firm granulations in the wounds, free from surrounding cellulitis. Bacteriologic studies have shown that it is probably easier to get sterile cultures from small wounds than from very large open areas. A thorough Carrel-Dakin technic is an advantage, but careful evaluation of the general condition of the patient and of the gross appearance of the granulations and the surrounding tissues usually suffices for determination of the time for operation. *Bacillus pyocyaneus* is one of the worst organisms to contend with in skin grafting but soap and water frequently applied, followed by 5 per cent gentian violet or a mercurial dye antiseptic, seems to give fair results (fig. 4).

Another important result from the use of the saline bath is that secondary contractures often will have been straightened out by the voluntary effort of the patient, without traction or restraints. Most patients are extremely grateful for the bath and realize their first comfort in it, and it has occasionally been a life-saving measure. There may be a bad reaction to it however and there is frequently an elevation of temperature. If any of the bad effects are too severe the bath may be omitted at least temporarily.

When out of the bath, patients can be kept comfortably warm in a covered bed with or without dressings. This allows free movement and makes the nursing somewhat easier. Electric lights may be strung above the patient to supply warmth, but they have nothing to do with the treatment.

Ulcers of the Leg—The problem of preparation includes rest in bed, elevation and elastic pressure support of the leg and mildly antiseptic wet dressings. When the patient comes in with a foul, dirty ulcer of the leg, often the first step is to put him in a bath tub and let him see how clean he can get himself with soap, water and a brush. Postoperative care is important for protection of the graft and support of the blood column. A minimum of two to three weeks of rest in bed should be given and then gradual activity allowed with the area firmly supported with a mild ointment and the leg carefully wrapped in an elastic bandage. This support is maintained until there is no question of trouble with circulation and edema.

Hands—For burns of the hands every effort is put forth to prevent the deep infection that will so rapidly fix tendons and joints and produce deformities that may never be overcome. The first treatment is soap and water cleansing and gentle debridement, then the hands are wrapped in fine mesh grease gauze and bandaged. A daily saline soak with further debridement followed by a new dressing is carried out until the wound is ready for grafting, when it is best to discontinue the use of grease dressings if possible. This method might be called surgical drainage, in contradistinction to the sealing of the areas with tannic acid or plaster of paris. Active movement should be encouraged during the soak, the fingers should be dressed apart and the entire hand should be kept in the position of function. Most burns will be ready for grafting in three weeks if tendons have not been exposed and frequently the single application of a split graft may be all that is necessary. If there has been an extensive, deep burn it is often advisable to "dress" the wound with a thick split graft as soon as the sloughs are separated and the granulations are clean, so that healing may stimulate active movement and articular fixation may be limited, secondary repairs may be done later, as necessary. On all dressings of the hand in which there is any question of circulation in the fingers the tips should be left open for inspection (fig. 4 B).

Neck—A short comment on this region may be worth while to state that free grafts will grow on the neck if close attention to detail and fixation of the first and subsequent dressings is given. Also one of the most important points for success is that the patient should be fed with a feeding tube through the nostril for four to six days after the operation to prevent chewing and swallowing as much as possible.

Pedicle Flaps—In the postoperative care of a pedicle flap there is often a question of its viability, that is, the maintenance of its blood supply. An adequate arterial supply is, of course, important, and if this fails little can be done. However, venous congestion, as expressed by general duskeness of the flap, will usually respond to a gentle pressure dressing which seems simply to keep the venous channels compressed. Massage and warm moist compresses have been recommended for this condition, but these are apt to produce more harm than good, and it is felt definitely that a gentle pressure dressing is as important for flaps as it is for a free graft.

Whatever permanent dressing is desired is applied, and then a separate pressure dressing of cotton waste is placed over the area of

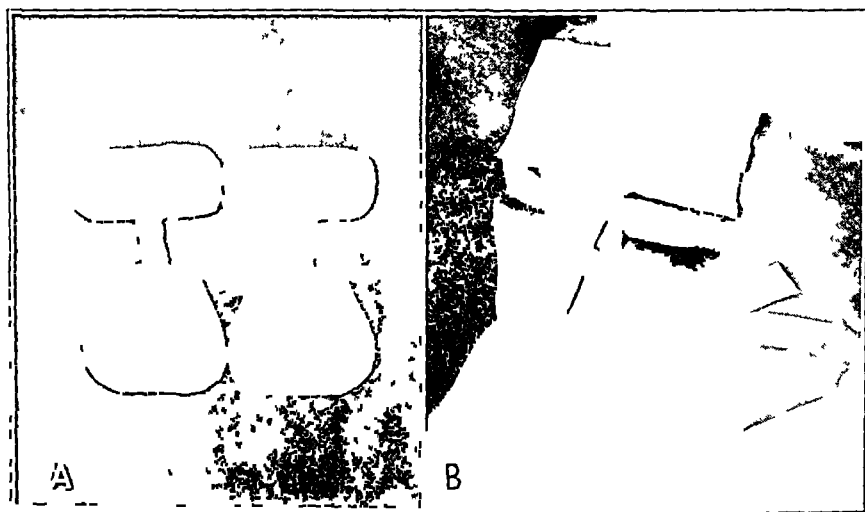


Fig 5—Sheet aluminum, 0.0016 inch thick, used for a nasal splint (A). It is covered with old linen held on with rubber paste, and the adhesive tapes on the cheeks supply gentle elastic pressure. The nasal part of the splint may be cut off and used on the nose, being held with rubber cement or collodion after fresh adhesive tape or gauze has been put over the splint (B).

attachment of the flap. Many flaps that are actually blue at the end of the operation will respond to this dressing. The flap should be observed and the dressing rearranged at hourly intervals as long as there is any question.

There is a form of central venous thrombosis that may occur in tubed flaps in an occasional patient, for which little can be done except to combat the infection that is usually the cause.

ROUTINE CARE OF FREE FULL THICKNESS SKIN GRAFTS

Cutaneous eruptions are contraindications to reconstructive operations especially, and patients are thoroughly examined for any sign of

them at the time of the regular physical examination and again on the morning of the operation. If large grafts are to be taken, the clotting time should be determined.

One should be sure that there is an adequate area of preparation, both in the field of operation and at the donor site. Hair should not be shaved from the abdomen or from the thigh if the graft is to be applied on the face, as these areas are hair bearing.

Dressing in Operating Room—The graft is covered with fine mesh grease gauze (scarlet red or bismuth tribismphenate [velotorn]) and then with plain gauze, cotton waste or a marine sponge is then placed over the entire area, and a pad is placed over it. A snug bandage is then applied so as to obtain an even elastic pressure over the whole graft. Extra care must be taken to immobilize the parts and adjacent joints and prevent slipping and to prevent vomitus from getting under the dressings (fig 2).

If satisfactory, this dressing is to remain in place six to eight days. It can then be removed and the stitches taken out. If the area is perfectly

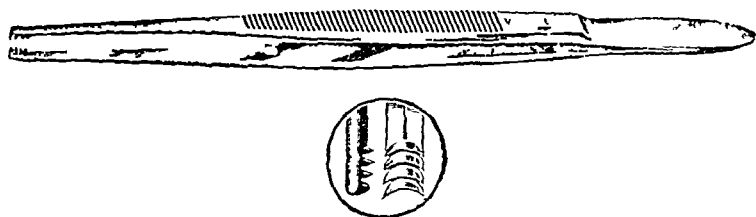


Fig 6—Multiple tooth forceps with the teeth running up the shank instead of across the end. This makes possible gentler grasping of tissue and, therefore, less scratching of the skin. The teeth will also steady a needle until it can be pulled through.

clean, the same type of dressing is reapplied, and there is no need of changing it for several days if there is no slipping and if no sign of infection is present.

If blebs occur, they should be opened and all dead epidermis removed. The area should be painted carefully with gentian violet or some suitable mild antiseptic. Sloughs should be removed where possible, especially so if pus tends to creep under them. If infection is present, wet dressings of boric acid or saline solution should be applied and kept moist at all times. A skin graft dressing should never be allowed to dry; it should either be kept moist or have a grease gauze dressing on it.

If blood clots are present, the graft is carefully incised, the clot is emptied if possible, and the edges of the skin are allowed to drop down in place. It is not necessary to trim the edges away unless they are infected.

ROUTINE CARE OF THICK OLLIER-THIERSCH OR THICK
SPLIT GRAFTS

The same care applies to the preparation of the patient and to the care of these grafts as to the full thickness ones except that, since they are apt to be put on dirty fields, they are usually to be dressed on the third to the sixth day and that the postoperative pressure does not have to be kept up so long.

The dressing is applied as under full thickness grafts if the area is considered clean enough.

Wet Dressings —If the graft has been put on an old ulcer or "x-ray burn" that is known to be unresponsive to treatment a wet dressing may be applied with plain fine mesh gauze next to the graft instead of the grease gauze and with the pressure dressing the same, but with tubes in the dressing to allow the addition of saline solution. This wet dressing, which has to be kept on three to four days, becomes messy and of bad odor, but it seems that grafts will succeed in some dirty fields in this way that would probably be lost with the regular grease dressing.

The sutures are usually removed at the first dressing, the dead, overlapping edges are cut away and either a grease dressing or a wet dressing is reapplied, as indicated by the condition of the graft and wound or by any surrounding cellulitis. If infection is present the dressing should be changed at least daily.

DRESSING THE DONOR SITE OF A THICK SPLIT GRAFT

Two layers of fine mesh grease gauze are placed smoothly over the area from which the skin is taken, and a small dressing is put over this and strapped firmly in place with adhesive tape, almost around the leg. This dressing, if done accurately and firmly, splints the part very well and in a sense replaces the skin that covered it. If it slips around or is loose, there will be a great deal of pain. The layer of gauze next to the skin should not be removed as long as it is stuck unless it can be soaked loose, its removal tears away the fresh epithelium under it, delays healing and causes extreme pain. A larger dressing can be put over this and the outer one changed before the end of nine days if necessary for cleanliness. Tannic acid and silver foil have also been recommended for use over the donor site. Tannic acid, however, probably acts by tanning, i. e., by killing live cells in the dermis, and is not used by us (fig. 2).

At the end of nine to twelve days there is usually complete healing, and no further dressing is necessary. If there has been infection or the graft has been cut too deep, there will be markedly delayed healing that will require daily care until epithelization is complete.

The donor site heals by a dedifferentiation of the epithelium in the deep glands of the skin. Healing occurs at varying rates for individual

patients and for grafts of different thicknesses. Infection seems actually to destroy the cells, and healing may take as long as six to eight weeks if infection becomes severe. Usually there is complete surface coverage with squamous epithelium at the end of six days but this will not stand any trauma for about twelve days.

PREPARATION OF COTTON MECHANICS WASTE AND MARINE SPONGES FOR PRESSURE DRESSINGS

The two types of waste illustrated have proved satisfactory for most dressings. The material is cheap, easily handled and much more easily incorporated in a dressing than are marine sponges (figs. 1 and 2).

The waste is obtained in bales of various size from Wiping Materials Inc., 2028 North Main Street, St. Louis or some similar company. The white variety is of shorter fiber and is bleached. The coarser material is unbleached and has longer threads so that it is used for larger dressings. The cost is 12 cents per pound.

The bale is autoclaved at 30 pounds (13.6 Kg.) of pressure for one hour, then it is opened and suitable amounts are resterilized in drums, jars or wrapped packages for handling at the time of operation. It is hoped to have manufacturers of surgical gauze supply this in large sterile packages to avoid the trouble of preparation and a "crinkled" gauze supplied by one of them is being tried at present.

Marine sponges should be of good quality, large, soft and "wool-form," and they should be bleached. Bleaching does not injure them, does not cost any more and helps in general in handling and in having the dressing appear clean. These are prepared by beating the loose dirt out, washing in soap and water and then soaking in 1:1000 mercuric bichloride or mercury cyanide for forty-eight hours, washing out in saline solution, allowing to dry out and putting away to dry. They should not be stored wet but can be kept in drums or sterile wrappers. They are, of course, remoistened to soften them when they are applied. The sponges are not to be handled by the clean nurse and are not to be put directly on wounds, because their sterility is only relative.

HOMOGRAFTING OF SKIN

Although it is definitely known at present that homografts of skin do not survive permanently, they will usually "take" successfully and persist for two to eight weeks. They are then slowly absorbed or thrown off but during the period that they are attached there is an improvement in the general condition of the wound and because of this with increased cleanliness there may be an actual stimulation to spontaneous healing.

For the foregoing reasons it may be expedient with some patients who are dangerously debilitated by large open burn defects to do homo-

grafts so that the wounds may be completely or partly closed temporarily and thus allow the patient a respite from his discomfort. This may be termed "dressing the wounds" in homografts and has proved life saving in some instances.

There is apparently no relation to blood grouping even down through the M and N groups, and, therefore, this does not have to be taken into account. (In one of the most dramatic cases in a large series the patient's life was thought to have been saved by this procedure, grafts were used from 26 donors at one time²).

When the homografts have disappeared, the wounds are usually much cleaner, smaller and less painful, the patient has gained from his respite of pain and increasing debilitation and the repair may usually be completed with grafts of his own skin.

As has been reported previously, it seems certain that grafts from identical twins should grow and survive permanently.

Occupational Therapy—This may play a most important part in the outcome of the operation both from a mental and a physical standpoint and is especially important for burned patients who are to have a long period of hospitalization. Together with this, physical therapy either voluntary or by directed active and passive manipulation, may be of great assistance in preventing and overcoming secondary stiffness of the tendons and joints (fig 4B).

TRACHEOTOMY ROUTINE

Patients with respiratory difficulty should be watched closely in the ward, and the surgeon in charge should be kept posted frequently, as sudden changes in the patient's condition and even sudden death are apt to occur. The tracheotomy set, procaine hydrochloride and gloves are to be ready at the bedside of the patient. The technic of tracheotomy should be known by the house officer in charge, and he should keep in close touch with the ward at all times.

These patients make a great effort to breathe, but they gradually wear out, morphine is not given, because it may be just enough of a depressant to the respiratory center to stop its function. Atropine is not given, because it may dry out the airway just enough to allow one part to stick to another and occlude the passage. Having steam in the room may help to keep the trachea moist. Light sedatives may be used with caution.

Tracheotomy should be done early and in the operating room if possible. If in doubt, one should open the trachea, any error should be made on this side. The pulse of the patient should be watched. If the

2 Drs Lyman Brewer and Alfred Gelhorn assisted ably and untiringly in caring for this patient.

rate goes up, it is probable that the heart is being taxed, and at this stage it is better to open the trachea than to allow the patient to carry on an uphill fight against the obstructed airway. It is preferable to open the trachea with deliberation so that careful dissection can be done, but regardless of how or when it is done the opening should always be below the first tracheal ring. To open higher may result in laryngeal stenosis. The thyroid isthmus may be cut through if necessary.

Moist inhalations and the use of ammonium chloride or potassium iodide may be advantageous if secretions are thick.

If there is any sign of heart failure, it is well to have medical consultation as to the advisability of digitalization.

If the patient swallows with difficulty, a feeding tube may be inserted through the nostril. However, the nurses should be advised about the danger of giving too much liquid at one time, as it is apt to regurgitate and overflow into the larynx. Small sips of water or cracked ice can still be taken by mouth. If the feeding tube further embarrasses respiration (before the trachea has been opened) it should be removed.

After the trachea is open, special instructions should be given to the nurses about keeping the inner tube clean and free of clots of blood. Pipe cleaners are easy to use, but any gauze or cotton that can be pushed through the tube with a probe will do. *Care of the Inner Tube.* It should be kept clean, it should be boiled at least twice a day and whenever else there is any special contamination. It should be scoured inside and out each morning. If there is obstruction to breathing even when the inner tube is clean, there may be a plug over the lower end of the outer tube, and, if so, the entire tube should be removed and cleaned. It may also be too short and may have slipped out of the tracheal opening.

If left in very long, the tube becomes foul, and the entire inside of the trachea will develop an offensive odor that is possibly due to a pyocyanous infection. The entire tube therefore, should be removed and cleaned as necessary. When the tube is out and being cleaned, care must be taken that the opening does not contract so that the tube cannot be introduced again. The time limit for keeping the tube out may not allow for sterilization and cleaning of the tube, and, if not it is necessary to have an extra tube on hand to put in as soon as the dirty one is removed. The obturator should be kept at the bedside ready for use any time the entire tube has to be reinserted. The dressing around the tube and the tapes should be changed as often as they become soiled.

In all manipulations of the tube one should be as gentle as possible. One should try not to touch the sides of the trachea with the lower end of the tube, as to do so irritates the area and starts violent coughing. Each time the inner tube is put back in a drop or two of green

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